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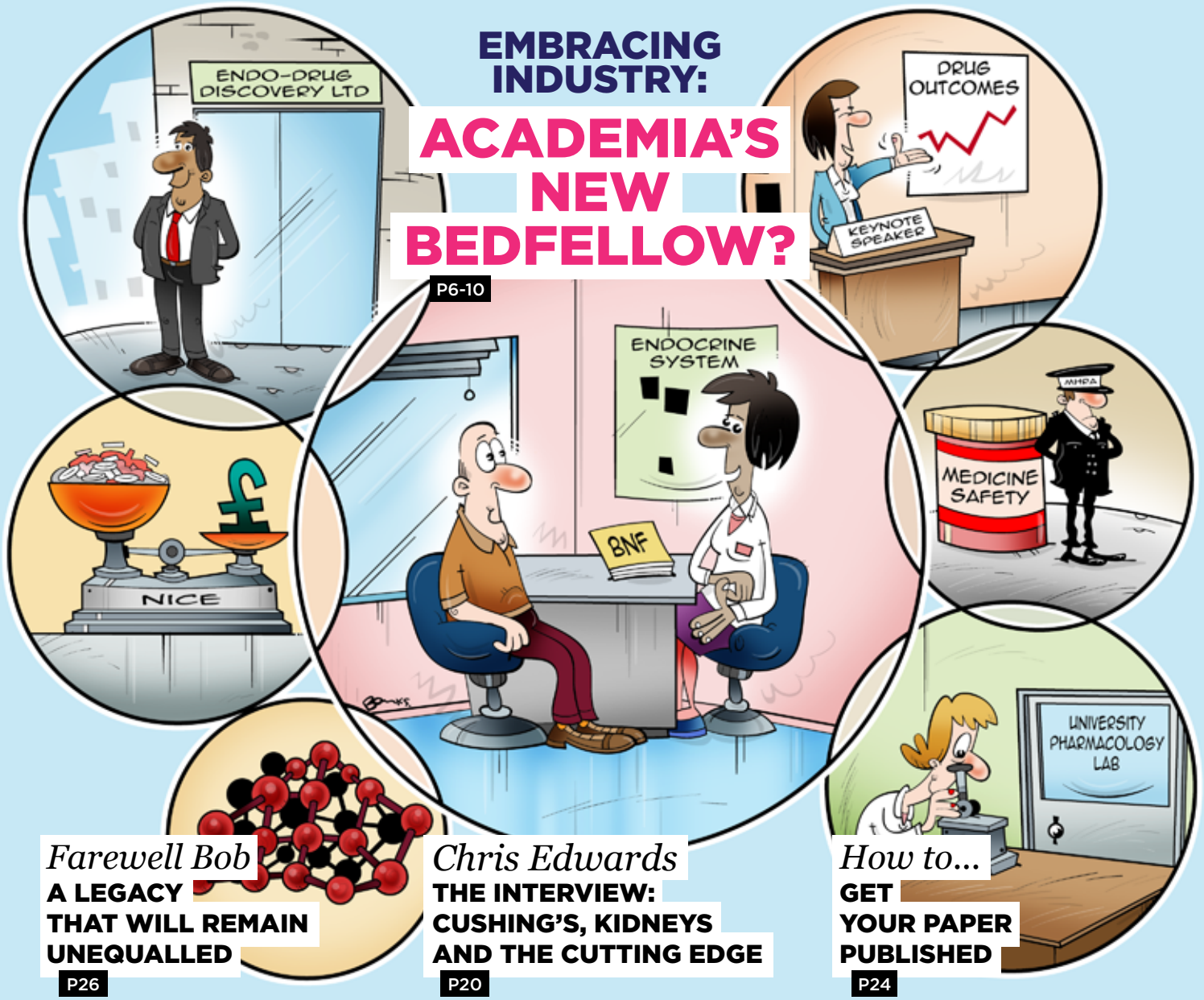
THE ENDOCRINOLOGIST

THE NEWSLETTER OF THE SOCIETY FOR ENDOCRINOLOGY



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A WORD FROM THE EDITOR...

As you sift through your post, I hope your copy of *The Endocrinologist* is starting to make its way into the 'don't throw away immediately and think about reading later' pile. You may (or may not) have noticed that each edition has a particular endocrine-related theme that we hope is relevant to clinical endocrinologists, basic scientists, patients with endocrine conditions, and those in any other walk of life who might be interested in our subject.

This season's theme covers how all our lives are affected by the pharmaceutical industry. My personal experience is that I have found myself constantly running out of pens and those sticky post-it things, which is most inconvenient (although it is difficult to explain why the pharmaceutical industry has hitherto felt the need to act as our stationers!). We are probably all a little squeamish about our interaction with pharma, but the relationship seems pretty simple – we need the best drugs to treat our patients, and drug companies need us to prescribe their products or they won't earn any money.

The problem comes if marketing is over-zealous and, as we are quite a discerning bunch, this always goes down badly. Basic science and clinical medicine are blessed with intellectual freedom (if not money!) and we are naturally a little weary of industry folk, whom we may regard as inherently biased towards their own product. However, the articles in this edition show the healthy state of endocrinologist–pharmaceutical company interaction, and demonstrate that our relationship is essentially a symbiotic and thriving one.

One of the pleasing things about this issue is that very senior people have written articles for us, which further raises the profile of the magazine (surely impossible, you cry). Please keep all your excellent ideas flowing so *The Endocrinologist* continues to go from strength to strength.

BEST WISHES
MILES LEVY

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www.endocrinology.org/endocrinologist

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Become a contributor...

Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the editor.
We would also like to hear your feedback on this issue of the newsletter.
The deadline for news items for the Winter 2013 issue has passed. Deadline for news items for the Spring 2014 issue: 20 December 2013.

KNIGHTHOOD FOR SOCIETY'S PRESIDENT-ELECT

The Society's President-Elect, Professor Stephen O'Rahilly, was awarded a knighthood for services to medical research in the Queen's Birthday Honours list. He is Professor of Clinical Biochemistry and Medicine at the University of Cambridge and Co-Director of the Wellcome Trust–MRC Institute of Metabolic Science. His research on human metabolic disorders has revolutionised our thinking on diabetes and obesity, in particular the role of genetic factors.

Speaking on the news of the award, Professor Sir O'Rahilly said, 'I am delighted to accept this honour on behalf of the many dedicated colleagues who have worked with me over more than 20 years to make Cambridge a centre of excellence for research and clinical care in the area of metabolic and endocrine diseases. Having lived in the UK for more than half my life, I am touched that the work I have been involved in has been recognised by my adopted country in this way.'

NEW COUNCIL MEMBERS NEEDED

Dr Steve Ball, Professor Karen Chapman, Dr Helen Christian and Professor Richard Sharpe will retire from Council in March 2014, having served their 4-year terms of office. Full Members are invited to make nominations for these positions. A nomination form is included with this mailing or can be downloaded from www.endocrinology.org/about/committee/council.html.

We seek to provide a balance of expertise on Council and are therefore particularly seeking three scientists and one clinician to fill the vacancies. The deadline for nominations is **12 December 2013.**

ENDOCRINE CONFERENCE WINS TOP PRIZE

The team receive their award

Big congratulations go to the Society's trading subsidiary, Bioscientifica, and the International and European Societies of Endocrinology for winning Best Association Conference at the Conference Awards 2013 for the 15th International and 14th European Congress of Endocrinology, which took place in Florence in 2012. As those of you who attended will know, this highly successful event brought together 5,500 endocrinologists from around the world to discuss the latest advances and network with colleagues. The judges commented, 'This was a complex large scale event which used novel and current marketing techniques to engage the target audience, and created a well respected industry event.' Well done to all involved!

SOCIETY MEMBER RECOGNISED BY ROYAL SOCIETY

We congratulate Society Member Professor Sir Stephen Bloom (London) on being elected to the Fellowship of the Royal Society. This is in recognition of his work establishing the physiological mechanism of the endocrine system in the gastrointestinal tract, leading to major developments in the search for obesity and type 2 diabetes treatments.

HONOUR FOR SOCIETY'S PRESIDENT

We are delighted to announce that the Society's President, Professor Ashley Grossman (Oxford), has been awarded the 2014 Geoffrey Harris Prize by the European Society of Endocrinology.

This prestigious award recognises Professor Grossman's significant contribution to the field of neuroendocrinology. It will be presented at the 16th European Congress of Endocrinology in Wrocław, Poland in May 2014, where Professor Grossman will also present a lecture detailing his work.

SOCIETY CALENDAR

4-6 November 2013
CLINICAL UPDATE
Bristol

6 December 2013
REGIONAL CLINICAL CASES MEETING
Belfast

25 Feburary 2014
NATIONAL CLINICAL CASES MEETING
London

24–27 March 2014
SOCIETY FOR ENDOCRINOLOGY BES 2014
Liverpool

see **www.endocrinology.org/meetings** for full details

GRANT AND PRIZE DEADLINES

1 November - 3 December 2013
FREE PLACES AT SOCIETY FOR ENDOCRINOLOGY BES 2014

27 November 2013
EARLY CAREER GRANT

15 December 2013
CONFERENCE GRANT

11 February 2014
UNDERGRADUATE ESSAY PRIZE

11 March 2014
SUMMER STUDENTSHIPS

see **www.endocrinology.org/grants** for full details of all Society grants

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society Members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via **www.bioscialliance.org.** *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access and free to all.

JOURNAL OF ENDOCRINOLOGY

Neuroprotection by melatonin and dexamethasone after brain trauma

The inflammatory response, immune mediators, breakdown of the blood-brain barrier, brain oedema and oxidative stress can cause neuronal loss days after initial brain trauma.

Campolo and colleagues investigated the therapeutic benefit of combined melatonin and dexamethasone following traumatic brain injury in mice. Melatonin has neuroprotective effects in other models of injury, perhaps related to its antioxidant and free-radical scavenging properties. Glucocorticoids have anti-inflammatory and immunosuppressive effects and are used to treat various inflammatory conditions. Melatonin combined with the synthetic glucocorticoid dexamethasone reduced brain oedema and infarctions, lesion size and apoptosis levels and facilitated improved motor function compared with monotherapy.

Targeting multiple pro-inflammatory pathways appears to give greater neuroprotective effects than single effector treatment. This strategy has also been beneficial in other tissues, and may prove efficacious for other inflammatory diseases.

Read the full article in *Journal of Endocrinology* **217** 291–301

JOURNAL OF MOLECULAR ENDOCRINOLOGY

Aldosterone down-regulates apelin expression

Adipokines, secreted by adipose tissue, have been implicated in obesity, diabetes, hypertension and cardiovascular disease. The adipokine apelin, and its receptor APJ, have beneficial effects on obesity-associated disorders and cardiovascular homeostasis. There is evidence that aldosterone can affect the adipokine profile; patients with primary aldosteronism show reduced leptin and adiponectin and increased resistin levels.

Jiang and colleagues investigated the regulatory effects of aldosterone on apelin expression and secretion. They found that mineralocorticoids and glucocorticoids down-regulate apelin expression and secretion through glucocorticoid receptor activation, suggesting the adrenal cortex regulates adipose tissue activity.

Further studies must determine whether the lower apelin levels found in hypertension, cardiovascular dysfunction or insulin resistance result directly from elevated aldosterone. However, this study suggests patients with high aldosterone levels may benefit from manipulation of the apelin–APJ system.

Read the full article in *Journal of Molecular Endocrinology* **51** 37–48

ENDOCRINE-RELATED CANCER

Hyperinsulinaemia promotes mammary tumour aggression

An association exists between diabetes and breast cancer, with hyperinsulinaemia linked to accelerated tumour growth. LeRoith and colleagues previously showed increased tumour growth in a mouse model of hyperinsulinaemia resulting from increased activation of the insulin receptor and the phosphatidylinositol 3-kinase/Akt/mTOR pathway.

The human epidermal growth factor receptor 2 (*Her2*) gene is overexpressed in 15–25% of female breast cancers and associated with a high risk of metastasis. Ferguson *et al*. evaluated the effect of hyperinsulinaemia on *Her2*-mediated breast cancer in a mouse model. They showed increased mammary tumour development and lung metastases, suggesting that hyperinsulinemia increases the tumours' metastatic potential and/or circulating tumour cell survival in the lung.

This provides a mechanistic insight into the association of hyperinsulinaemia with mammary tumour aggression and suggests that increased insulin receptor (IR/IGF1R) activation leads to increased tumour growth.

Read the full article in *Endocrine-Related Cancer* **20** 391–401

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Bringing CLARITY to structural analysis of the brain

Imaging a complex 3D structure such as the brain to a level that allows analysis of the intact pathways and networks is challenging. In a tour de force of bioengineering, Chung and colleagues describe a process termed 'CLARITY' to transform intact tissue into an optically transparent construct that preserves native structure. By fixing and supporting the structure with an acrylamide-based scaffold and then removing lipid bilayer, antibody labelling and immunohistochemistry can occur in the fully assembled organ, and the images generated are quite breath-taking.

As well as results from mice, the paper describes fine structural analysis of human brain tissue that has been stored in formalin for over 6 years. Quite aside from the images' aesthetic quality (the embedded video links are things of beauty), this technique is a leap forward in tying together structural and molecular analysis, and has potential for use across a wide range of tissues.

Read the full article in *Nature* **497** 332–337

Essential role of Tbx3 in pituitary development

The development of the anterior and posterior pituitary lobes is highly integrated and involves signalling gradients of factors such as the *Shh* gene product, fibroblast growth factors and bone morphogenetic proteins. These signals activate an array of transcription factors that determine the commitment and differentiation of progenitor cells. Hence, the pituitary is an excellent model system in which to investigate the patterning and development of complex tissue structures.

Tbx2 and Tbx3 are transcriptional repressors that direct patterning and cellular differentiation in many organs. In this article, Trowe *et al*., using lineage tracing methods, show that both Tbx2 and Tbx3 are expressed in posterior lobe progenitor cells. Analyses of knockout mice demonstrated that Tbx2 is not required for pituitary development, whereas Tbx3 was crucial for the formation of the infundibulum and the posterior lobe. The effects of Tbx3 deficiency potentially resulted from a failure to repress the transcription of *Shh*, which, in addition to the effects seen in the posterior lobe, also disrupted the development of the anterior lobe.

Read the full article in *Development* **140** 2299–2309

Hot Topics is written by Tony Coll, Karen Featherstone, Paul Foster, Paul Grant and Olympia Koulouri.

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

MTC and duodenal calcitonin-secreting NET

Huguet *et al*. report a 63-year-old woman with a 1cm thyroid nodule, identified as medullary thyroid carcinoma (MTC) by fine needle aspiration biopsy. Following total thyroidectomy with lymph node clearance, MTC was confirmed by histology. However, her calcitonin levels remained elevated. Detailed cross-sectional and functional imaging failed to detect local recurrence or distant metastatic spread.

After 3 years, she had a gastroscopy to investigate iron-deficiency anaemia. Biopsy of a duodenal polyp showed evidence of a neuroendocrine tumour (NET), which was removed by distal duodenectomy and shown to stain strongly for calcitonin. Subsequently, her calcitonin levels normalised. Genetic analysis for germline mutations of the RET oncogene was negative.

This is the first reported case of a duodenal NET secreting calcitonin, and of a second tumour secreting calcitonin in a patient with MTC. Association of the two pathologies seems plausible, but the mechanism is unknown.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* 2013 EDM130021

CLINICAL ENDOCRINOLOGY

Genetic predisposition to phaeochromocytomas and paragangliomas

Jafri *et al*. report the first extensive UK-based genetics study in patients with non-syndromic phaechromocytomas/paragangliomas (PPGL) and head and neck paragangliomas (HNPGL). In total, 501 individuals with PPGL/HNPGL were prospectively recruited over 10 years.

Testing included mutation analysis for the SDHB, SDHD and VHL genes. Almost one-third of patients with PPGL and two-thirds with HNPGL had a mutation. Mutations (mainly SDHB and SDHD) were most common in patients with positive family history, young age, malignancy, multiple tumours and extra-adrenal disease.

However, even 'low risk individuals' harboured mutations at a significant rate (29% of patients with a solitary, benign adrenal phaeochromocytoma), indicating a need to set specific criteria for testing in this group. The authors advocate an age cut-off of 45–50 years to balance out acceptable mutation detection rates and costs, but this should be reviewed as genetic testing becomes cheaper.

Read the full article in *Clinical Endocrinology* **78** 898–906

ENDOCRINE CONNECTIONS

Guideline evaluation for vitamin D supplementation

Vitamin D is derived from the diet or by conversion of cholesterol in the presence of sunlight. In 2011, two conflicting reports were published on vitamin D intake requirements. One, by the Institute of Medicine, specifies an estimated average requirement of 400IU/day, whilst the Endocrine Society's Clinical Practice Guidelines (CPG) recommend a 3- to 5-fold higher intake of 1,500-2,000IU/day.

McKenna & Murray have analysed 41 studies to assess whether differences between the guidelines were due to the mathematical approaches used to estimate the vitamin D dose response. They found that the CPG underestimate the vitamin D rate constant by 2-fold. This, combined with other factors, indicates that the Endocrine Society's CPG could lead to vitamin D over-replacement for many patients, with potential harm for some.

Read the full article in *Endocrine Connections* **2** 87-95

A role for glucagon in the brain?

Glucagon has long been recognised to act upon the liver to promote endogenous glucose production. Mighiu and colleagues have demonstrated that glucagon acting in the mediobasal hypothalamus (MBH) can inhibit hepatic glucose production in rodents. This effect was not seen if the action in the MBH was inhibited pharmacologically, or if glucagon was delivered to animals which had undergone a hepatic vagotomy. Interestingly, the ability of glucagon to act in the MBH to lower hepatic glucose production was lost in rats fed a high fat diet.

Although the physiological relevance of glucagon's effect in the human brain is yet to be established, it may be that central glucagon resistance plays a part in the metabolic phenotype often seen with obesity.

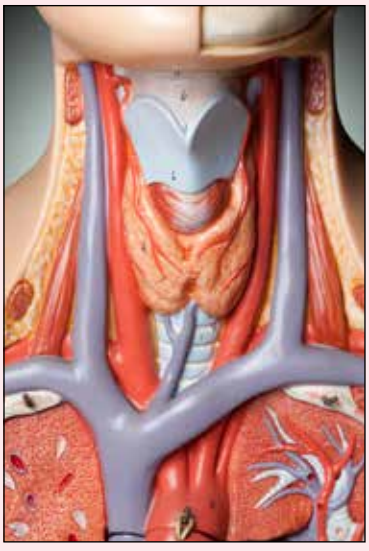
Read the full article in *Nature Medicine* **19** 766–772

How to treat low-risk papillary thyroid cancer

The incidence of papillary thyroid cancer is rising in many parts of the world. Most cancers of this type are small and generally regarded as low risk. However, in a subset of patients, the disease appears more aggressive and recurrence is more likely.

It is a challenge clinically to demonstrate that there are benefits to the traditional treatment approach of total thyroidectomy, ablation of remnant tissue with radioactive iodine and thyrotrophin suppression with exogenous thyroxine. There is a lack of evidence for such treatments because there are few good quality randomised controlled trials. This recent review by McLeod *et al*. discusses the controversies in the management of this type of thyroid cancer, summarises epidemiological data for disease incidence and looks at a treatment framework grounded in the best available evidence and existing recommendations from clinical guidelines.

Read the full article in *The Lancet* **381** 1046–1057



COLLABORATION WITH INDUSTRY

WRITTEN BY DAVID RAY

Those of us engaged in biomedical research are facing unprecedented competition for funding. Government agencies are interested in outputs beyond scientific interest, and request a detailed analysis of likely beneficiaries of funded work, along with specific details of how such benefit will be conferred, and also measured. At the highest levels of Government there is anxiety about the apparent crisis of UK-based big pharmaceutical companies, currently the sector with the greatest research and development spend in the British economy.

There is an obvious connection between these two agendas. If the UK Government is spending on biomedical research, then the commercial exploitation of that research requires industry, and naturally benefits industry. Effective co-operation between these two biomedical research funding streams offers an attractive economic justification for Government-funded research, but also helps to retain industry in the UK, and provides immediate, tangible economic benefits to the UK economy.

THE INDUSTRY VIEW

In the biomedical research landscape described above, what is the industry perspective? Lessons can be learned from the recent decision by AstraZeneca to relocate research and corporate functions to the biomedical research powerhouse of the Addenbrooke's campus in Cambridge. Explicit in this plan is far closer co-operative working between scientists on both sides of the industry fence. This suggests a new model of business whereby industry will re-cast itself as drug development rather than drug lead discovery.

In other words, industry is now seeking to abandon the ambitious plans of the past, which resulted in huge pseudo-academic campuses being established, and huge intramural discovery programmes, which in many cases never saw the light of day. This activity resulted in the generation of huge resources in terms of data sets, chemical biology tools, and technical expertise. In some cases, assets so developed were 'parked' within the company, not being developed, published, or made available externally. Such assets were overvalued, and the secrecy surrounding their existence represented a massive missed opportunity.

MITIGATING RISK

This is now being addressed by visionaries within industry, including Tim Willson at GlaxoSmithKline (GSK). He has opened the doors to the GSK tool compound collection for the broader research community to take a look. His model works on the basis that, should a clear pathway to exploitation open up, GSK would probably win the race against any academic operation, and so both sides would benefit, with negligible risk to the company, or to our pension funds invested in it!

A further approach to de-risking early phase, high-risk discovery science is the embedding of industry scientists within UK universities. In Manchester, we benefit from such an arrangement with GSK, whereby Stuart Farrow, a long-term colleague and friend, is now based with us nearly full-time, under an umbrella agreement covering intellectual property. Such initiatives offer hugely improved flexibility to industry, and greatly increase the efficiency of scientific discovery.

ACADEMIC OPPORTUNITIES

Of course, within academic institutions, the commercial exploitation of discoveries is also attractive, and now, for many academics, a call to their intellectual property and exploitation divisions is mandatory before publication. In this way, value can be retained around a discovery, leading to formation of a 'spin-out' company, which in turn provides a vehicle to hold intellectual property, and venture capital funding.

It is a long way from forming a spin-out company to getting a product to market, and many such enterprises will fail, with others being acquired by big pharma following due diligence. There are many examples of successful commercial exploitation and subsequent marketing of discoveries using this approach, including monoclonal antibodies targeting tumour necrosis factor for inflammatory conditions.

LOOKING AHEAD

So what will the future hold? The persistence of monolithic companies with an intramural programme extending from basic biology through to marketing products seems questionable. The demands of modern science, the requirements for expertise in specific areas of biomedicine and the rapid cycling of new technologies suggest a breakdown to smaller functional units with stronger ties into the broader biomedical discovery enterprise. These units are likely to form and disband with shorter cycles of operation, resulting in a leaner, more nimble portfolio of active research.

The expectation with this approach is that greater access to industry resources for those training in basic biomedical science, or clinical research training fellows, will benefit both sides, and that schemes to encourage free exchange of staff back and forth across the industry/academic divide will also be mutually beneficial. How such collaborative activity is recognised by host institutions in this day of metrics collections and league tables will require thought.

So the future is very different from the past, but new opportunities arise to meet new threats, and are out there to be grasped!

DAVID RAY
Professor of Medicine and Endocrinology,
University of Manchester

David Ray is General Secretary of the Society for Endocrinology, and Deputy Chair of the MRC Clinical Research Training Fellowship Panel. His interests in nuclear receptor function and inflammation, circadian biology and energy metabolism have led to extensive links with industry, notably GSK, who funded him with a personal fellowship in 1998–2003.

DISCLOSURE: THE SECRET BEHIND SUCCESSFUL COLLABORATION

WRITTEN BY DAVE GILLEN

Over the last 30 years, advances in medical therapeutics across multiple specialties have helped revolutionise medicine. These advances have been possible largely because of close, effective scientific and clinical collaborations between clinicians, academics and industry.

Despite this, particularly over the last 10 years, the relationship between the aforementioned key collaborative stakeholders has been described as hostile, confrontational, distrustful and controversial. Over the years, some examples of poor practice have led commentators to describe the relationship as badly damaged or even broken.[1]

A CODE OF PRACTICE

In response to concerns, legislators around the world have put in measures to improve the transparency of the relationships between doctors and pharmaceutical companies. In the UK, companies are bound by the Association of the British Pharmaceutical Industry (ABPI) Code of Practice Authority, which produces a Code of Practice to which companies in the UK adhere.[2]

'Over the last 10 years, the relationship between the key collaborative stakeholders has been described as hostile, confrontational, distrustful and controversial.'

The 'Code' is a voluntary set of rules with the aim of ensuring that the promotion of medicines to healthcare professionals is carried out appropriately within a robust framework. Soon after its inception, the ABPI recognised that, for the Code to have credibility, the industry could not regulate itself directly. An independent body – the Prescription Medicines Code of Practice Authority (PMCPA) – was created to administer the Code on behalf of the pharmaceutical industry, which it does at arm's length from the ABPI.

Each country regulates its pharmaceutical industry in different ways, and while the UK Code has much in common with its overseas relatives, it is the oldest (over 50 years old) and the most rigorously enforced. For example, whenever there is a complaint regarding the behaviour of a company, the details of the investigation are published in full by the PMCPA. Serious transgressions actually result in fines, corrective statements and advertisements in key medical journals such as the *British Medical Journal*. Other sanctions include audits of a company's procedures to comply with the Code, followed by the possibility of a requirement for the pre-vetting of future material and ultimately suspension or expulsion from the ABPI.

INCREASING TRANSPARENCY

The recent revision of the ABPI Code of Practice came into operation on 1 January 2012 and includes a number of steps designed to increase 'transparency' with regard to the financial support provided by the industry to healthcare professionals.[2] The particularly relevant changes for doctors include the requirement that payments in relation to donations and grants, meetings, hospitality and sponsorship, and the use of consultants, are made public for payments made in 2012 and each calendar year thereafter. Disclosure is required in the calendar year following the year in which the payments were provided, and the information has to be made public (usually via a company's website) within 3 calendar months of the end of the company's financial year.

Details of each institutional grant or donation must be disclosed, in each case giving the financial amount or value and the name of the recipient institution, organisation or association. Similar transparency requirements exist for registration fees and sponsorship of UK healthcare professionals and appropriate administrative staff which are paid by pharmaceutical companies for them to attend meetings in the UK and overseas. Currently, this information must be disclosed as the total amount paid in a calendar year in respect of all recipients, and the total number of recipients. As yet the names of the recipients need not be disclosed, but this will change in the next few years as European regulations take effect.[3]

DECLARING FEES

Companies must also make publicly available details of fees paid to consultants in the UK, for certain services rendered by them such as chairing and speaking at meetings, assistance with training and participation in advisory boards etc. Lastly, details of payments made to doctors in relation to market research must be declared (unless the company is not aware of the identities of those participating in the market research). Fees and expenses and the like must be declared whether paid directly to the consultant or to their employers or to companies or charities etc. Currently the transparency requirements in the Code do not include payments to consultants in relation to research and development work, including the conduct of clinical trials.

'In our experience, doctors are comfortable with the increasing transparency, and I hope that these changes will allow the essential relationship to work again.'

Other changes in the Code designed to enhance openness include new checks on clinical trial transparency, and updated information about relationships between pharmaceutical companies and patient organisations. To date, in our experience, doctors are comfortable with the increasing transparency, and I hope that these changes, as well as others, will allow the essential relationship I mentioned at the start of this article to work again (if perhaps a little differently from the past), and help bring forward new innovations that will improve the outlook for patients.

DAVE GILLEN
Medical Director,
Celgene UK and Ireland

REFERENCES

1. Royal College of Physicians 2009 http://bit.ly/16DygCZ.
2. Association of the British Pharmaceutical Industry 2012 http://bit.ly/11W2DF2.
3. European Federation of Pharmaceutical Industries and Associations 2013 http://bit.ly/16Dymut.

TO SPIN OR NOT: THE CHOICE IS YOURS

WRITTEN BY RICHARD ROSS

So, you've come up with your big research idea, and you're confident it's a winner. But, what next? With the focus now on translational projects, most of our scientific ideas have commercial potential. To support your work, do you try for research council funding, or will there be greater gains from spinning-out your scientific strategy? Richard Ross provides his insights into the world of the spin-out company.

In 1999 I took a 6-month sabbatical in Sydney, Australia. At that time, I was struggling with raising grant income and felt a sabbatical would allow me to reflect and possibly change direction to better-funded pastures. Taking a sabbatical, in one of the world's most beautiful cities, enriched my life in ways that were both unpredicted and unexpected.

I love reading fiction. In Sydney, I joined a creative writing course and the first term was entitled 'unlocking creativity'. Seminars were held above a vegetarian restaurant in Bondi Junction, and I was only one of two men among a group of predominantly young women.

LOSING INHIBITIONS

At first I was inhibited, scared I would embarrass myself, felt arrogant to presume anyone would listen to me and worried that I would expose some unattractive aspect of my personality in my writing. I quickly learnt we all had the same anxieties and no-one cared what I wrote, they just wanted me to listen to their story. It was a liberating experience.

Letting the pen flow opened up the concept of risk: taking the risk of expressing myself, believing in my ideas and recognising the value of creativity in both literature and science. The outcome was a medical thriller under my mother's maiden name (*Tolerance* by Richard Roseveare, available from Amazon) and the founding of two spin-out companies, Asterion Ltd and Diurnal Ltd.

RAISING FUNDS

A major positive outcome from commercialising my ideas was raising money for my research. Asterion raised venture capital and I signed a licence agreement to develop a long-acting growth hormone. Diurnal raised venture capital and EU funding to develop new hydrocortisone formulations, Chronocort® and Infacort®, for the treatment of congenital adrenal hyperplasia and adrenal insufficiency.

With this funding, our group has published papers and taken a drug from the bench to phase II clinical studies with the potential of a product reaching the market in 2016. I have learnt new words such as 'milestone', which have created greater discipline in my work. I have collaborators across the world, and work with an exceptionally talented group of drug developers. It has been a roller coaster experience with a few highs, signing investment and licence agreements, and plenty of scary lows, including rejected patents and pharma partners changing strategic direction overnight and so halting drug development.

THE ROUGH AND THE SMOOTH

A challenge for me was getting buy-in from the university and understanding from investors. Despite the university owning part of the companies, I wasted more time than I would like to remember arguing over research contracts, and I was blocked from grants as the company owned the intellectual property. On the other side of the fence, some investors had limited understanding of academic research and wasted time with complex financial negotiations.

The climate is changing with the new 'impact agenda'. I have been able to use my experience to build a team of business managers within the University of Sheffield Healthcare Gateway to support academics commercialising their research.

Would I spin again? Yes, I love the creativity in commercialising research. At heart I am an academic and, now that my work is aligned with the university strategy, my energy is being used to maximum benefit. Whether I will make any personal money is yet to be seen, but I would counsel others not to see that as a main goal. The risks in drug development are high and at Sheffield University you are more likely to make money in a licence deal with less pain.

To spin-out a company you need to believe in your idea and commit yourself to commercialising it.

RICHARD ROSS
Professor of Endocrinology, University of Sheffield

MOVING TO PHARMACEUTICAL MEDICINE

WRITTEN BY MARISSA SEE

Pharmaceutical medicine is a fledgling specialty, officially recognised in the UK in 2002. It was not familiar to me when I decided to leave clinical practice some years ago.

My reasons for leaving were many – if I had to choose one, it was to broaden my horizons beyond NHS walls. I discovered the pharmaceutical industry through a friend, and moved to a role as a medical advisor in medical affairs.

OPPORTUNITIES IN THE INDUSTRY

Pharmaceutical medicine covers every phase of bringing a drug to market that involves patients and public health. Broadly speaking, these are clinical development (pre-licence), regulatory affairs (licensing), medical affairs (post-licensing) and drug safety/pharmacovigilance (throughout).

The common route into the industry is through medical affairs, unless you have specialist expertise in another area. Pharmaceutical physicians in medical affairs are trained in the Association of the British Pharmaceutical Industry's Code of Practice, and ensure the ethical promotion of medicines through adherence to the Code. A role in medical affairs balances commercial exposure with an interest in science and patient care.

Consider clinical development if you are interested in clinical trials and drug development, particularly if you have knowledge of this area. You can gain experience by working for a contract research organisation, managing trials for pharmaceutical companies. Regulatory affairs and pharmacovigilance tend to require some relevant prior knowledge, and medics entering these roles often have industry experience.

CAREER PATH

I joined a pharmaceutical company which was small in size, but in the global top 25 in terms of revenue. My choice was deliberate – you get a lot more exposure to all aspects of the industry in a small company. This comes with the challenge of fewer resources compared with big organisations; I was the only doctor in the company for several years. I chose to do an executive MBA at the London Business School to consolidate my understanding of the commercial aspects of the business and to broaden my network.

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SPECIALTY TRAINING

Specialist training in pharmaceutical medicine is managed by the Faculty of Pharmaceutical Medicine, which was established in 1989 and part of the Royal College of Physicians. It takes a minimum of 4 years culminating in a certificate of completion of training, and is an accepted part of the revalidation process. There is a requirement to complete the Diploma in Pharmaceutical Medicine as part of the theory exam.

I now head a team of ten, and am part of the senior leadership team at my company.

CONSIDERATIONS

For those contemplating a move into pharmaceutical medicine, I suggest you consider the following issues:

Timing – make the move earlier rather than later. Unless you have specialised expertise for clinical development, everyone starts at the beginning, which is ST3 equivalent.

Choose the right job – think about what you wish to achieve. Different companies offer different opportunities. It is not advisable to change jobs in less than 18 months unless there is a truly valid reason.

Specialist training and revalidation – it is not necessary to complete specialist training or to retain your licence to practise in order to work in the industry, although it is recommended. When accepting a role, make sure the company is supportive if you intend to pursue this.

Location – most companies are located around the M25 or in the research and development hub around Cambridge. Field medical roles do not require a medical degree and can be more commercially focused.

The choice to leave clinical practice for a career in pharmaceutical medicine has been the right one for me. I have achieved the broader exposure I desired, and have made good progress. For the future, I can choose to remain on the medical side and gain more strategic experience in European and global roles, or move to other areas, such as market access or even a more commercially focused position.

MARISSA SEE
Head of Medical,
Otsuka Pharmaceuticals (U.K.) Ltd

CHANGING FACE OF COLLABORATION: INDUSTRY VIEWS

Recently the pharmaceutical industry has shifted from blockbuster drugs to more personalised medicines, with companies working collaboratively with partners from academia, the NHS and elsewhere. Here, some of the Society's Corporate Supporters share their thoughts on this shift in the marketplace.

bioscientifica

Bioscientifica supports the advancement of medicine and the biological sciences redistributng our profits to champion the global scientific community and the drive for better public health ... purpose *beyond* profit. Specifically, as the Society for Endocrinology's commercial subsidiary, we partner a number of bioscience organisations, assisting in the delivery of advocacy support, policy, education, events, publishing and association management activities for the wider dissemination of endocrine knowledge.

Our ongoing work for the biosciences community has created many supporting frameworks and initiatives which contribute to the growth, development and enhancement of our partnerships with the NHS and other international health organisations. Under a vision to 'engage, support, advance', Bioscientifica continues to collaborate extensively with the NHS and beyond to address the challenges of increasing public understanding of hormone-related conditions, whilst providing increased support for clinicians, basic scientists, nurses and allied health professionals at all career stages.

Bioscientifica holds a unique position; as an independent organisation we act as an honest broker, bringing together various stakeholders in this dynamic and changeable environment to enable the development of novel strategies to deliver improved patient outcomes.

IPSEN Innovation for patient care

Factors which drive collaboration in the pharmaceutical industry include new treatment discovery, clinical development (perhaps the one most familiar to you), and the impact of innovative new medicines on patient outcomes and healthcare resource utilisation. Ipsen is very active in all these collaboration areas with clinical partners.

Ipsen is a global specialty-driven pharmaceutical company with its development strategy focused in endocrinology, neurology and uro-oncology. Ipsen's R&D is focused on its innovative and differentiated technological platforms of peptides and toxins. This is further supported by an active partnership policy with academic institutions and innovative biotechnology companies, with the aim to transform scientific advances into therapeutic advances for patients.

A recent example of such an approach is the 3-year collaboration and subsequent acquisition of Syntaxin, a UK-based private life sciences company and leader in recombinant botulinum toxin technology. Syntaxin's recombinant toxin expertise and Ipsen's know-how will be a powerful combination to release the full potential of the Targeted Secretion Inhibitors platform across Ipsen's therapeutic disease areas including endocrinology.

In the UK, Ipsen is also collaborating on several projects in support of the on-going major reorganisation in the healthcare delivery, the drive to deliver efficiencies in the care pathway including 'care closer to home' whilst improving patient outcomes and 'the patient experience'. Such collaborations include the sponsorship of registries which may be used to evaluate clinical outcomes in growth disorders and gastroenteropancreatic neuroendocrine tumours, and the provision of care in the home services which help improve patient experience and efficiency of care delivery.

HRA Pharma

Since entering the field in 2002, HRA Pharma has been an active member of the rare endocrine diseases community, investing in, developing and supporting the enhancement of medical treatments and services for patients suffering from rare endocrine disorders.

In 2002, HRA Pharma obtained orphan status in Europe for a key product indicated for the symptomatic treatment of advanced adrenal cortical carcinoma and, in 2004, the product was launched across Europe. HRA Pharma also developed Lysosafe, a free of charge therapeutic monitoring service that helps clinicians optimise the treatment of patients receiving this product.

In 2011, the company reinforced its engagement in the endocrine field by acquiring a product already well-established in the UK for the management of Cushing's syndrome. HRA Pharma is currently investing in research for this disorder, with a view to expanding the current knowledge base and optimising patient management.

SANDOZ

Sandoz, a Novartis company, is committed to collaborative working with the NHS and other healthcare providers to ensure that the products and services we bring to market are relevant, useful and help to improve access to affordable high quality biopharmaceuticals. Competition breeds innovation, and the closer we are able to work together, the more chance there is that new developments will truly meet the needs of healthcare providers and bring meaningful developments for patients.

In the field of endocrinology, Sandoz Biopharmaceuticals, together with input and insights gained from practising physicians, nurses and patients, have developed and launched their own new injection device, designed specifically for patients requiring that therapy, as well as developing an award-winning patient support programme.

With our expansive research and development programme, Sandoz Biopharmaceuticals is committed to working collaboratively with all UK stakeholders, including patients, to help bring to market the next generation of biosimilar therapies to further transform patient care and patient outcomes through innovation, improved access to therapies and individualised support.

ViroPharma™

A rare disease is defined in the European Union as a life-threatening or chronically debilitating condition that affects no more than 5 in 10,000 people and adrenal insufficiency is one example. In the UK approximately 3.5 million people will be affected by a rare disease at some point in their lives. These people may benefit from new innovative treatments that could support improvements in their quality of life and help deliver better outcomes.

For patients to access new innovative treatments, adequate funding is needed. In England, this responsibility lies with (a) NHS England, whose ambition is to bring equity and excellence to the provision of specialised care and treatment and (b) clinical commissioning groups (CCGs) who are responsible for nearly 60% of the NHS budget and have a role regarding ongoing management. Scotland and Wales have, or are exploring, alternative mechanisms for funding rare diseases.

ViroPharma is an international biopharmaceutical company committed to helping people with rare and potentially life-threatening conditions, by developing innovative products to try and help address unmet medical needs.

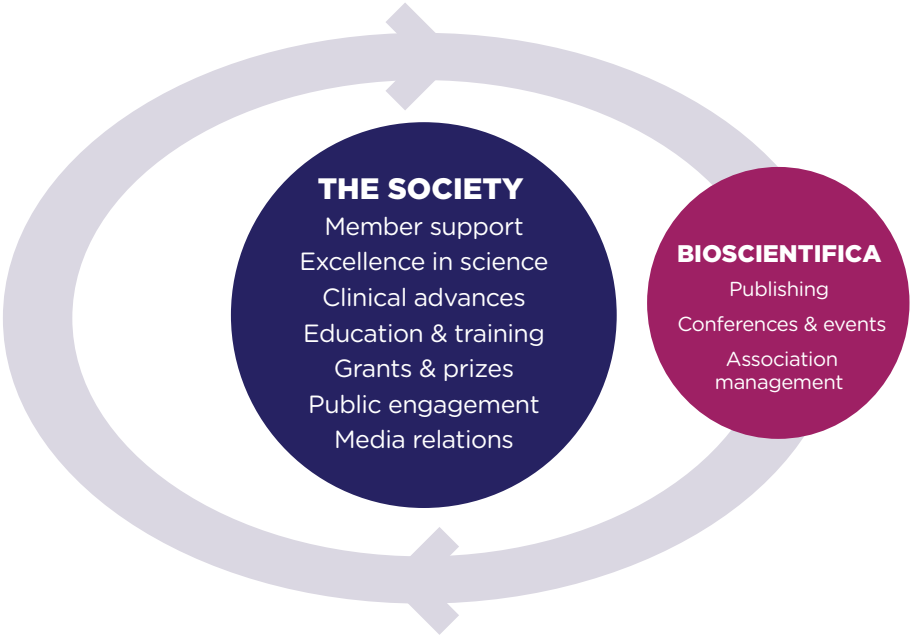
FROM THE CHIEF EXECUTIVE'S DESK: COLLABORATION CLOSE TO HOME

WRITTEN BY LEON HEWARD-MILLS

Society for Endocrinology

The Society and Bioscientifica are two organisations with a shared purpose – to improve knowledge, health and life.

bioscientifica



A theme of this issue of *The Endocrinologist* is collaboration with industry, and this calls to mind a collaboration closer to home – between the Society and Bioscientifica.

The relationship between the Society and Bioscientifica is not always clear – as attested by several conversations I've had with Members on this topic over the last 2 years. Why is the organisation split? What's the real benefit? Who owns who?

Some of our recent work has tried to clarify this – to show the distinct nature of the two organisations: one a charity with a clear remit to advance endocrinology for the public benefit, one a commercial organisation offering services to learned societies and industry across endocrinology and related disciplines, but the two with a shared purpose – to improve knowledge, health and life.

Bioscientifica is the Society's company. It is wholly owned by the Society and any profit it does make is gifted to the Society each year, supporting our grants, educational activities and patient support work – our core charitable activities. Having a separate commercial arm means the Society can focus on delivering these core objectives without added distractions or conflicts of interest, but it also safeguards the Society in the long term by providing a source of income separate from other more variable sources – subscriptions or donations.

Between 2009 and 2012, Bioscientifica has delivered nearly £3 million to the Society. The Society in turn has delivered £1.8 million to Members, patient groups and others in grants alone over the same period.

Much of Bioscientifica's profit derives from its publishing activities – publishing the Society's journals and working with other endocrinology-related societies. It is worth noting, however, that 80% of publishing income comes from academic and commercial institutions outside the UK and mainland Europe.

Bioscientifica's Conferences Division also demonstrates what is possible through collaboration, winning the 'Best Association Conference of 2012' at the 2013 UK Conference Awards, for the ICE/ECE in Florence (see page 3). This is a major achievement, and one that has reflected well on the group as a whole – Bioscientifica promoting excellence in its own field to ensure the underpinning of future Society activities.

But that's all well and good. The question from a Member's point of view is what is this profit for? Profit or growth for its own sake is not meaningful. Development must be appropriate, and in line with the Society's core aims – advancing endocrinology for the public benefit.

With the current challenges to the profession and the pressures on science at home and abroad, there is a greater need than ever to ensure that we fulfil our charitable remit, build on scientific excellence and increase the support we are able to give to Members, patient groups and the public. Our current focus sits squarely across these areas.

To safeguard our investment we have to be prudent – investing where appropriate to ensure that Bioscientifica diversifies and can continue to provide the returns we need, and managing costs and risk across both the Society and Bioscientifica effectively.

The collaboration with Bioscientifica allows the Society to develop in an appropriate way and it will, I hope, ensure the success of the Society for many years to come.

LEON HEWARD-MILLS
Chief Executive, Society for Endocrinology and Managing Director, Bioscientifica Ltd

DOING THE RIGHT THING

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

The most important thing I was told on joining the lab was to tell the truth. The message was clear – once someone starts making things up, we might as well all go home. Great, got it.

In the same week, the most memorable thing I was told was not to talk about any of the mouse-based projects outside of work. People 'might not understand', they might 'get upset', it could be 'dangerous'. Oh ... OK, sounds bad. Best not then.

Problem is, omission can inexorably lead to mistrust and presumption of misdeed and, in any field of research, inadequate reporting of what was done is harmful. That an equally skilled peer should readily be able to reproduce the experiment is critical for credibility. A failure to replicate a finding because of mis- or lack of information from the primary source is wholly avoidable and, however annoying that might be if the cell cultures were only fit for the bin, if this futile experimental venture had involved animals, it's not hard to see how feelings might run high.

Research involving animals has always been an emotive subject. This is right and proper, because it's too important an issue to attract anything other than vigorous thought and debate. It also deserves robust regulation and close scrutiny. When done properly, it can be incredibly powerful, and great tranches of endocrinology have benefited from insights based on animal studies. Alternative experimental platforms should always be considered, but when trying to understand how whole networks of tissues integrate with each other, the study of an endlessly passaged, immortalised cell line may not be meaningful.

Mindful of the fact that we aim always to educate and inform regarding all aspects of our endocrinological activities, the Science Committee have recently endorsed the ARRIVE guidelines (www.endocrinology.org/policy). Take a look and you will see they outline a useful framework for thinking about how *in vivo* experiments should be reported. In doing so, they aim to reduce unnecessary repetition, facilitate better design and maximise quality and impact of the data presented.

It's been a trying time for openness of late. Publicly funded bodies set up to inspect hospitals, or spy on the bad guys, or work out if new drugs might damage the organ they were supposed to support, have fallen into a tangled mire of denial and blame, all leading one to feel uneasy about finding the truth through the murk. However, giving an honest and dispassionate account of all that we do in our scientific environment sounds to me at least a small step in the right direction.

TONY COLL

For more information on the ARRIVE guidelines, visit **www.nc3rs.org.uk/ARRIVE**

FULL SPEED AHEAD

FROM OUR CLINICAL COMMITTEE CORRESPONDENT

It's been a busy time since I succeeded Peter Trainer as the Society's Clinical Committee Chair in January 2011. Great change within the Society has seen a 'resetting' of its strategic objectives, including this Committee's activities.

We on the Committee, who represent the consultant and trainee body within both the NHS and academia, seek to enhance high quality clinical endocrinology practice across diverse settings and subspecialties. To do this, our remit is broad, and includes:

- **Enhancing recruitment to the specialty**, influencing undergraduate and postgraduate training and exposing students and junior trainees to the many interesting aspects of endocrine practice. We work with other bodies to protect postgraduate training in endocrinology from inroads from acute and general medicine.
- **Supporting the Society's meetings portfolio**, including the highly successful Clinical Updates, the Clinical Cases meetings and, of course, the Society BES, indirectly improving training and standards of practice through these activities.
- **Supporting peer review visits** to endocrine units, to allow dissemination of good practice and to support colleagues working in challenging environments.
- **Developing clinical management guidelines** for a variety of endocrine disorders, frequently the less common conditions.
- **Providing guidance for day to day practice**, including for colleagues in other specialties, by developing advice for endocrine emergencies (see page 16).
- **Ensuring appropriate representation of endocrinology** among professional bodies driving clinical practice.
- **Enhancing advancements in endocrinology** by supporting audit and research projects, especially multicentre activities.

Society BES 2013 was especially busy for the Committee, which steered gatherings to address postgraduate training issues, chaired by Peter Selby as Chair of the Special Advisory Committee for Endocrinology and Diabetes Mellitus and involving regional training programme directors.

We launched a group to review the Society's research and audit projects policy and discussed the establishment of new 'Endocrine Networks', soon to be open to all Members (see page 16), which will build on the excellent work of the Special Interest Groups. Our aims include improving grant capture for studies of endocrine disorders and enhancing engagement in our Members' research.

Our meetings have addressed the pressing issue of treatment of adrenal insufficiency and the sometimes poor management of acute adrenal crises, including the need for updated guidance and a 'revamp' of the outdated steroid card.

At the end of my tenure, I hope we will be able to see that we have supported high quality clinical practice through better training, guidance, peer support and research and audit. And we will have had a lot of fun along the way, thanks to my fantastic colleagues.

JAYNE FRANKLYN

KITE SURFING, 10,000 HOURS AND MASTERY

WRITTEN BY JOHN NEWELL-PRICE

Have you ever tried kite surfing? You have to marvel at this improbable activity and the extraordinary skill, style and panache displayed by the riders. Those attending ENDO 2013 in San Francisco will have been treated to the sight of swarms of the multicoloured kites highlighted by the late evening sun, set against the iconic Golden Gate Bridge silhouetted in the distance.

"How would you go about acquiring this alien skill?... Ultimately, you'd have to take the plunge: sign up for some lessons, and, importantly, get wet."

Every second, a series of extraordinary skills is coalesced in order to execute this mind-boggling pastime: skimming across the water whilst balancing on a plank that has no buoyancy; controlling a kite that generates sufficient force to be capable of catapulting the operator tens of metres into the air and dislocating all manner of joints; being hyperaware of all opportunities to refine speed and poise; responding to shifting wind directions; and avoiding obstacles, including other water traffic ... and the occasional shark!

How would you go about acquiring this alien skill? You might gain some insight by watching some YouTube videos and spending evenings researching kit and technique. However, ultimately, you'd have to take the plunge: sign up for some lessons, and, importantly, get wet. Initial attempts would be challenging, scary and frustrating, but with perseverance, correct guidance and, most importantly, dedicated practice and application, you would eventually be an expert.

In the face of limited availability of time, if you really concentrated on technique on every occasion that you went out on the board, the level of your mastery would increase greatly, and more quickly. Back this up with theory of the technique, and the results would be even quicker. With the right exposure and luck you might even get a sponsorship deal, join the world competition circuit and be chosen to grace a Red Bull advert – whilst for most people simply participating in the sport would be an excellent and rewarding end in itself.

You will have recognised this thinly veiled analogy to medical specialist training. Expert clinical endocrinologists are the kite surfers of the medical world, integrating reams of data in a careful and timely manner with the necessary great attention to detail, and using knowledge and skilful clinical acumen that other specialties frequently wonder at.

Reaching such status is, however, under threat. Currently, a major source of frustration is the detrimental effect on endocrine training caused by the demands of the acute medical take and continuing care. The solution to this very important problem lies outside the control of endocrinology, as it can only be solved by multi-specialty re-engagement with general internal medicine, so sharing the burden that all too often falls disproportionately on our trainees. This issue is high on the agendas of the committees of the Society for Endocrinology and Royal Colleges, but will take time to resolve.

The oft-quoted 10,000 hours needed to master any discipline is relevant, with the distinction between competence and mastery being key. Early on there is a steep learning curve, whilst the latter part is finessing. It's a long time: one that for many will extend beyond clinical specialist training. Of course, not all experience is equal, and some areas are easier to master than others.

How then, today, does one maximise the opportunities to learn and gain experience in the current time-limited training environment? One answer is the postgraduate course. For example, the Society for Endocrinology runs the excellent and highly rated Clinical Update, an annual 3-day residential course that covers the training curriculum over 3 years, and where participants have the opportunity to closely interact with, learn from, and challenge experts in their field: experts who are so motivated to teach and impart knowledge and transfer skills that they give their time freely and generously in what are always hectic schedules.

Courses are important, but are not the complete solution. There is one very simple, free, and time-efficient strategy that can be used to maximise the experience of clinical training, but one that has, perhaps, become less commonly practised – learning from each and every patient. By this I do not mean to invoke some trite soundbite that might appear in some educational rubric, nor a series of acronyms beloved of the ARCP process, such as CBD, miniCEX and DOPS.*

"One very simple, free, and time-efficient strategy can be used to maximise the experience of clinical training... learning from each and every patient."

No, I am simply stating that, for every single patient that one has not seen personally before, the set of notes (especially if thick) should be opened at page one, and read ... to completion. This takes some time but always yields results, and with practice the skill becomes quicker. Unanswered issues (e.g. imaging, biochemistry and pathology) are then chased up and a complete picture generated. It is surprising how often this is not done, and then how rapidly answers to a clinical problem appear when it is. Add in background reading for a given condition, and, like the emerging kite surfer dedicated to practice, mastery grows organically.

JOHN NEWELL-PRICE
Reader in Endocrinology
and Honorary Consultant Physician,
University of Sheffield

John Newell-Price is a Reader in Endocrinology and Honorary Consultant Physician at the University of Sheffield and Sheffield Teaching Hospitals NHS Foundation Trust. He is also the Programme Co-ordinator for the Society for Endocrinology's Clinical Update series, Chairs the Joint Specialist Committee for Endocrinology and Diabetes for the Royal College of Physicians and is Training Programme Director for SpR training in South Yorkshire.

*For those new to these acronyms: Annual Review of Competence Progression (ARCP), featuring Case-Based Discussions (CBD), mini-Clinical Evaluation Exercises (miniCEX) and Direct Observation of Procedural Skills (DOPS).

GET THE MOST FROM YOUR MEMBERSHIP

Membership of the Society for Endocrinology makes a strong statement about you. It shows your employers, peers and patients your commitment to your specialty and identifies you as a professional who is serious about staying informed, educated and involved in endocrinology. Moreover, the benefits and opportunities that your membership provides for you as an individual are what makes us one of the foremost endocrinology societies in the world.

There are many reasons to join the Society. For some it is about wanting to keep up to date with the latest clinical support or endocrine-related research, whilst for others it may be the opportunity to share best practice and network with peers.

Regardless of where you are in your career – a student taking your first tentative steps on the proverbial ladder, more established and steadily climbing, or at the top of your profession – membership of the Society comes with a plethora of ways to aid your advancement.

For instance, central to the future of our profession is the next generation of clinicians, nurses, and research and clinical scientists, and the Society is proud to boast an increasing number of trainee endocrinologists among its membership. In addition to having access to early career grants, awards, practical skills grants, summer studentships and conference grants to attend the Society's meetings and those of other endocrinology societies across the world, trainee endocrinologists state that one of the most important aspects of their membership is the sense of remaining in touch.

The feeling of isolation during periods of concerted study can be alleviated by the Society's regular news updates, which enable Members to keep up to date with developments and stay in touch with other endocrinologists at the same time. This sense of 'contact' is resonant throughout our entire membership.

Indeed, the further along we progress in our careers, the more importance we place on the need to network with our peers and share best practice. The Society's global community of endocrinologists, for example, is cited as one of the primary reasons why Members stay with us, with the opportunity to forge often invaluable contacts with peers throughout the world, and share information, experiences and build fruitful collaborations. That's not forgetting adding their support to the Society's lobbying activity, discounted registration fees at all Society for Endocrinology meetings and training courses, and free online access to the Society's journals, to name but a few of the wide range of benefits available to all Members.

Membership can mean different things to different people and, thanks to your continued support, we can continue to nurture the next generation of endocrinologists, support our Members at all stages of their careers, influence Government policy and – more importantly – help shape the future of public health. The Society for Endocrinology is the voice of the profession.

If you have a colleague whom you feel would benefit from becoming a Member of the Society for Endocrinology, please refer them to our website: www.endocrinology.org/membership.

DEANNE NICHOLLS, Society Services Executive

UNDERGRADUATE ESSAY PRIZE WINNER

The winner of the Society's 2013 Undergraduate Essay Prize of £1,000 is Lucy Simmonds (Nottingham) for her essay 'The long term harm of a life-saving treatment – is it worth running away from?' (read the full essay at www.endocrinology.org/grants).

We also awarded six prizes of £250 to the runners-up: Philippa Bowes (Brighton), Andrew Dooley (Oxford), Eliz Kilich (Oxford), Grace Petrovic (Cambridge), David Whiteside (London) and Tianying Zhang (Cambridge).

This year's competition attracted a record 88 entrants. Each submission was marked and ranked by a distinguished panel. We were very impressed with the high quality of essays. Congratulations to all the winners!

ENTER OUR 2014 COMPETITION

Are you an undergraduate with a passion for endocrinology? Why not consider entering our 2014 Undergraduate Essay Prize competition? You could win £1,000! The application deadline is 11 February 2014. Find more details at www.endocrinology.org/grants.

CONGRATULATIONS

We are delighted to announce that Society Member Rebecca Reynolds has been awarded a Personal Chair in Metabolic Medicine at the University of Edinburgh.

VOICE OF YOUNG SCIENCE

In June, five Young Endocrinologists attended a workshop held by Sense About Science's young scientist network, Voice of Young Science (VoYS). These workshops provide attendees with the tools to interact with the media effectively, whether when commenting on a new piece of research or taking action against bad science. The Society will provide a number of priority places for Members at future workshops, and travel grants to attend. Check our website for future announcements.

We are pleased to be an annual supporter of VoYS – find out more at www.senseaboutscience.org/voys.

IN FESTIVAL MODE

WRITTEN BY TOBY STEAD

Edinburgh International Science Festival

Science festivals: where the Jimi Hendrixs and Beyoncés of the science community gather to interact with the public in all manner of formats.

Spring and summer have seen us attending science festivals across the country. Travelling first to the colourful city of Brighton, we took part in 'Big Science Saturday', a whole day of presentations from some of the top minds in the country. Here, Stephen Shalet (Manchester) took to the stage to present 'The Seven Ages of Man', an endocrine critique of Jaques' monologue from Shakespeare's *As You Like It,* which famously catalogues man's life in seven stages.

Weaving through growth stages in infancy, puberty (which, Stephen noted, Shakespeare seems to have glossed over), adulthood, middle age and the eventual and inevitable metabolic decline in old age, Professor Shalet captivated the audience. Turning the tables, the audience held him captive with an extensive and diverse Q&A session including growth hormone dynamics on starvation diets, and the menopause and hormone replacement therapy (HRT).

Second on our programme was the Edinburgh International Science Festival. Now in its 25th year, the festival invited us to give a two-course presentation on the obesity epidemic. Providing 'the main', Tony Goldstone (London) outlined the many factors that have combined to create today's toxic environment. His own work using brain and body imaging was employed to the full in describing the psychology and physiology that dictate our route through the obesogenic environment.

Providing 'dessert', Edinburgh's own Jonathan Seckl bravely attempted to steer a future course. A journey through his own work demonstrated a clear need to address a rising trend in obesity, as epigenetic inheritance of abnormal metabolism, and obesity's impact on cognitive aging and cardiovascular health, warn against inaction. But what of the options? Here things got more complicated, and an appraisal of bariatric surgery, pharmaceuticals and simpler but less effective lifestyle interventions showed that there is unlikely to be one solution to this multifactorial problem.

Our third instalment took place at *The Times* Cheltenham Science Festival, where broadcaster Vivienne Parry chaired two lively sessions. The first, 'Hormone Fight Club', saw three experts debating their views of the most important hormones. Waljit Dhillo (London) was first up, with a case for gut hormones. He explained the critical role of endocrinology in seeking a solution to the obesity epidemic. When the bell rang, Anne-Lise Goddings (London) gave her case for sex hormones and their influence on the brain and risky behaviour through adolescence and adulthood. Ding ding! Last was Stafford Lightman (Bristol), whose presentation arguing for the importance of cortisol matched the others for content and, with the winning blow, featured a musical representation of hypothalamic-pituitary-adrenal rhythmicity over a 24-hour day. I've never heard anything like it!

The next day we returned with Steven Franks (London), Saffron Whitehead (London) and Helen Buckler (Salford) for 'Menopause: to HRT or not HRT'. Given the controversy and confusion that this topic has seen, it was unsurprising that a large crowd gathered. Professor Franks began with an outline of the physiology behind the menopause and the accompanying symptoms. Professor Whitehead followed with her extensive research into the history of HRT, from its beginnings as an 'elixir for life' and through the ups and downs in the media and scientific literature. Dr Buckler closed with the state of play today regarding HRT's risk–benefit balance.

We thank all those who gave up their time to speak at and chair our events.

We are currently working on plans for science festivals in 2014. If you have an idea for an event or would like to volunteer to help us, contact toby.stead@endocrinology.org.

TOBY STEAD
Public & Media Relations Executive

Crowds gather at Cheltenham Science Festival

Do you have an idea for an activity to bring the public into contact with endocrinology? Apply for a Society Public Engagement Grant of up to £1,000!
See **www.endocrinology.org/grants.**

INTRODUCING ENDOCRINE NETWORKS: THE SOCIETY'S NEW ENDOCRINE COMMUNITIES

The Society for Endocrinology has recently announced a revision of its existing Special Interest Groups (SIGs) and the introduction of a new assembly of Endocrine Networks.

Each Network will become a community in its own right, where experts can benefit from a more robust environment for promoting and sharing best practice and knowledge and exchanging experiences with peers within their respective fields of expertise. This should provide each Network with greater visibility and influence compared with the existing SIGs.

In addition to continuing to provide daily news alerts, online discussion forums, message boards and blogs, the new Endocrine Networks will actively recruit trainee Members to become involved in various Network activities. A new central fund has been created to support these activities. In a move to encourage Members to hold meetings and seminars at local institutions that are accessible to individuals based around the country, Endocrine Networks will be actively encouraged to apply for the Society's Sponsored Seminar grants.

Underpinning this entire development is a determination to increase the level of engagement among the Society's subject specialists. The new Endocrine Networks will serve as a source of ideas and encourage a higher level exchange of information which will influence a wide range of activities, from meetings and symposia to guideline proposals for the Clinical Committee and the provision of patient engagement/information through the Public Engagement Committee, for example.

As the Society continues to move forward, so too does its on-going support for Members at all levels. The new Endocrine Networks will not only benefit from increased funding, they will provide Members with even greater opportunities to engage with and support colleagues, whilst helping to advance the pace of discovery in endocrinology.

Watch this space for more details!

For further information contact debbie.willis@endocrinology.org.

SOCIETY FOR ENDOCRINOLOGY EMERGENCY ENDOCRINE GUIDANCE

Endocrine emergencies, a group of potentially life-threatening conditions, are often overlooked when they first present in the emergency setting, as they require a high level of clinical suspicion for diagnosis. If these endocrine disorders are not rapidly identified, or if specific treatment is delayed, significant complications or even death may occur.

While many symptoms would be recognisable to trained endocrinologists, they would be less familiar to an acute medical admitting team or staff in an accident and emergency department.

To address this issue, the Society's Clinical Committee has begun a new initiative to introduce concise and easy to follow guidance documents, for use in emergency situations, where prompt management may be life-saving. Three *Emergency Endocrine Guidance* documents have been developed to date: pituitary apoplexy, acute hypocalcaemia (adults) and acute hypercalcaemia.

Pituitary apoplexy is a medical emergency caused by haemorrhage and/or infarction of a tumour within the pituitary gland. A high level of clinical suspicion is essential to diagnose this condition, as prompt management may be either life- or vision-saving.

Acute hypocalcaemia (the guidance is for use in adult patients) is a life-threatening condition that necessitates urgent treatment. The commonest cause of the condition is disruption of parathyroid gland function, but other causes include severe vitamin D or magnesium deficiency. In severe cases, intravenous calcium forms the mainstay of initial therapy, but it is essential to ascertain the underlying cause and commence specific therapy as early as possible.

Acute hypercalcaemia, when severe, requires urgent correction due to the risk of dysrhythmia and coma. Under physiological conditions, serum calcium concentration is tightly regulated. Abnormalities of parathyroid function, bone resorption, renal calcium reabsorption or dihydroxylation of vitamin D may cause regulatory mechanisms to fail and serum calcium to rise.

Each *Emergency Endocrine Guidance* document has been written on the basis of the evidence available and extensive professional experience, and has been peer-reviewed by the Society's Clinical Committee. The Society aims to distribute the documents as widely as possible to non-endocrinologists and emergency departments using its network of contacts, including Society Members, the College of Emergency Medicine, the Society for Acute Medicine, the Royal College of Physicians, and NHS Trusts.

The guidance documents can be downloaded from the Society's website at www.endocrinology.org/policy. To request a printed copy, please contact rachel.austin@endocrinology.org.

Information for the general public and patients regarding the conditions covered by each guidance document is provided on the Society's public website, You & Your Hormones (www.yourhormones.info).

CLINICAL EXCELLENCE AWARDS

The Society congratulates Karim Meeran (London), Neil Hanley (Manchester) and John Newell-Price (Sheffield) on receiving Clinical Excellence Awards in the very competitive 2012 award round.

CLINICAL ENDOCRINOLOGY EDITORIAL BOARD: CALL FOR NEW CLINICAL TRAINEE MEMBER

The Society's official clinical journal *Clinical Endocrinology* is looking to appoint a new clinical trainee member to the Editorial board to start in January 2014. This venture reflects our desire to maintain the journal's relevance for clinicians at all levels of experience. The new appointee will play a key role in developing new educational resources linked to journal articles.

To apply, please contact Professor John Bevan at johnbevan@nhs.net, attaching a mini-CV (no longer than one A4 side) indicating your present post, stage of training, clinical interests, research experience and previous publications (select up to three). Describe the skills and contributions you feel you would bring to the Editorial board. The deadline for applications is **15 November 2013**. More information is available at www.endocrinology.org/news.

JOURNAL OF MOLECULAR ENDOCRINOLOGY AT 25: RIDING THE TSUNAMI

WRITTEN BY ADRIAN CLARK

Endocrinologists were at the forefront of the molecular biological revolution. The cloning of the genes encoding insulin, growth hormone and pro-opiomelanocortin, for example, were landmark events that provided new insights into biology and endocrine science. The ability to measure specific mRNA abundance, albeit only semi-quantitatively, and to demonstrate that hormones affected the transcription of genes – something we now take for granted – set the foundations for radical advances in biology.

A surge of endocrine research was taking shape by the early 1980s, but the methods remained complicated. The development of the polymerase chain reaction (PCR) in 1988 and, importantly, the hardware and reagents required to perform it, was a giant step forward. It was at exactly this time that the Society for Endocrinology took the decision to launch a new journal, *Journal of Molecular Endocrinology* (JME), specifically to support this newly expanding discipline of molecular endocrinology.

A multitude of important and well-cited papers appeared in JME over the ensuing years. However, so much of endocrinology concerns precise measurement of dynamic changes that it is highly appropriate that the newly developed technique of real-time PCR – the gold standard of RNA quantitation – became a major focus of research in the journal, as evidenced by the publication in JME of Bustin's authoritative description of this highly influential technique in 2000 (**25** 169–193).

View a selection of the seminal papers published in JME by visiting **www.try-jme.org.**

After 25 years, and over 1,700 papers, JME has come of age, and is now celebrating its role in this extraordinary era of endocrine progress. As part of this celebration, we have commissioned a series of articles from major contributors to the field, which is guest-edited by Ron Evans – a scientist whose own contribution to molecular endocrinology over this time has been enormous. Keep an eye out for this special edition in an upcoming issue of JME.

The ability to perform and understand the molecular sciences has expanded markedly since 1988, and it is now typical to find the use of molecular methods in most endocrine science papers. So, is the need for a specialist molecular endocrinology journal now coming to an end?

I am certain that the answer is no. New molecular techniques are constantly evolving and emerging and, until their application becomes commonplace, they will need publishing in a dedicated journal. JME is that journal.

Furthermore, a second molecular torrent is now building in endocrinology, as a result of the incredible technology to collect huge amounts of molecular data from tiny samples, even single cells, at low cost. The new and massive challenge is to be able to make sense of this deluge of 'big data' far more effectively, so we can integrate genetic, epigenetic, transcriptomic, proteomic and metabolomic data in a constructive manner. JME certainly has to play a role in this next tsunami.

ADRIAN CLARK
Editor-in-Chief, Journal of Molecular Endocrinology

DONALD MUNRO

Professor Donald Munro died in May 2013 at the age of 88.

Though born in London, Donald was always extremely proud of his Scottish ancestry, and it is no surprise that he chose the University of Aberdeen to study medicine. After qualification, he served in the Royal Army Medical Corps in what was then Malaya. It was there that his career in teaching medicine started.

He was appointed as Lecturer in Pharmacology and Therapeutics at the University of Sheffield in 1953. Apart from his Fulbright Fellowship in Boston, he remained loyal to and proud of his adopted city, becoming the first Sir Arthur Hall Professor of Medicine and also heading the Medical School for a period as Dean.

His initial research focused on sodium metabolism in endocrine disease, but he then began a career-long series of meticulous studies on the newly discovered long-acting thyroid stimulator. Donald's group was one of the first to show that this stimulator was in fact an autoantibody, and that the levels of this in pregnant women with Graves' disease correlated closely with the probability of their offspring having neonatal thyrotoxicosis.

He was an excellent mentor and fostered the careers of many endocrinologists, including Pat Kendall-Taylor, Bernard Rees Smith, Colin Hardisty and Steve Tomlinson. He was a President of the Thyroid Club, the Endocrine Section of the Royal Society of Medicine and the Association of Physicians.

He established the Clinical Sciences Centre at the Northern General Hospital site in 1979, and also set up a novel computerised thyroid follow up scheme which continues to this day.

Donald was an exceptional endocrinologist who handled a phenomenal clinical workload while undertaking pioneering studies with technically challenging bioassays. It was entirely typical of his academic dedication that he chose to go on a sabbatical, to the lab of his friend Jack Martin in Sydney, after rather than before retirement. This was to complete his studies which showed that thyroid-stimulating antibodies can mediate effects through calcium signalling as well as cyclic AMP.

Donald was a deeply thoughtful and meticulous clinical scientist who inspired all those who met him. His wife Helen, who was a consultant radiotherapist, predeceased him; he leaves 4 children and 9 grandchildren, of whom he was extremely proud.

ANTHONY WEETMAN
University of Sheffield

ONE-STOP THYROID LUMP CLINIC

NEXT INSTALLMENT

WRITTEN BY FIONA GUY

I read with interest Katherine Powell's article 'One-stop thyroid lump clinic' (*The Endocrinologist*, issue 106, Winter 2012/13), and wish to update you on our 'One-stop radioiodine therapy and thyroid lump service' at Singleton Hospital, Swansea.

The thyroid clinic runs weekly and was introduced by consultant endocrinologist Dr Keston Jones, approximately 15 years ago. The medical physics department for the area is on-site, and the clinic is also supported by cytopathologists and respiratory physiology technicians.

The catchment area for the service is south west Wales, with a population of around 800,000, and includes a number of small towns and rural areas. Some patients have to travel up to 100 miles for their appointment. About 350 new patients are assessed each year, of which 140 will receive radioiodine therapy on their first clinic visit and 100 will undergo 'thyroid biopsy' by fine needle aspiration cytology (FNAC).

ONE-STOP THYROID LUMP SERVICE

Advantages of this service include patients receiving the result of their 'biopsy' at their first clinic attendance, which reduces the anxiety of waiting for the report and avoids unnecessary second clinic visits. Those who undergo FNAC are given the report within 1 hour. Patients with 'inadequate samples' will undergo repeat FNAC at the same clinic visit. Approximately 3–4% of patients are strongly suspected to have malignant disease following their initial FNAC, and further investigations or surgical referral can be organised immediately.

Patients with large goitres suspected of having upper airway obstruction undergo respiratory function testing, including flow volume loop, and receive the formal report at their initial clinic visit.

ONE-STOP RADIOIODINE THERAPY SERVICE

Referring consultants and general practitioners will have organised thyroid function tests prior to clinic attendance. Patients on anti-thyroid drugs (carbimazole or propylthiouracil) will have received a letter advising them to stop this medication 4 days prior to outpatient attendance, to enable treatment on their first clinic visit. Those who are likely to receive radioiodine therapy will have been sent a patient information leaflet regarding treatment and advised to travel to the hospital by private transport. They will also have been advised to make appropriate family arrangements and, if necessary, to consider arranging time off work following outpatient radioiodine therapy.

Following clinical assessment and signing a consent form, patients attend the radiopharmacy for outpatient radioiodine therapy. Medical physics colleagues order radioiodine on a weekly basis, depending on the number of patients expected to attend clinic.

NURSE ROLE AND AFTERCARE

I am the clinical nurse specialist for endocrinology for the Health Board attending the one-stop thyroid clinics. Part of my role is offering general support, answering questions patients may have, and ensuring they understand what is happening and what is expected of them at each stage of their investigation and treatment. My contact details are also given to the patient, to help address any subsequent worries or concerns – patients say that this service is invaluable.

Following initial clinic attendance, those who receive radioiodine therapy are either followed up in the Singleton thyroid clinic or by the referring consultant. Those requiring surgery are referred to an experienced thyroid surgeon.

IN SUMMARY

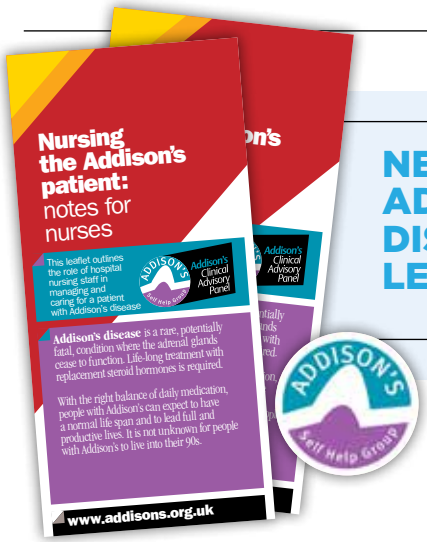
Our 'one-stop thyroid service':

- reduces the need for unnecessary clinic visits
- reduces travel time and inconvenience for patients
- reduces time off work for patients and relatives
- reduces patients' anxiety, as they receive FNAC results on their first clinic visit
- enables rapid patient assessment and treatment

This form of service could be introduced on hospital sites which have a medical physics department, supportive cytopathologists and respiratory physiology technicians. Our service is unique in Wales, and I would be interested to know if a similar service exists in the UK, as I am not aware of one.

FIONA GUY
Endocrine Clinical Nurse Specialist, Abertawe Bro Morgannwg University Health Board, Singleton Hospital, Swansea

Send your views on one-stop thyroid services to ***endocrinologist@endocrinology.org.***



NEW ADDISON'S DISEASE LEAFLET

The Addison's Disease Self Help Group is pleased to announce the launch of their new leaflet aimed at nurses.

'Nursing the Addison's patient: notes for nurses' was written by their Clinical Advisory Panel and outlines the role of hospital nursing staff in managing and caring for a patient with Addison's disease. The leaflet can be downloaded free of charge from www.addisons.org.uk or obtained by email at info@addisons.org.uk.

ECE 2013 HERALDS NEW ESE NURSES' GROUP

WRITTEN BY PHILLIP YEOH

Spring 2013 saw a formal nurse programme at the European Congress of Endocrinology (ECE) for the second time. It was very well received by more than 100 attendees from a wide range of disciplines, during ECE 2013 in Copenhagen, Denmark.

The 'Meet the Nurse Expert' session allowed endocrine nurses from different countries to share their expertise. It was followed by a Nurse Symposium on congenital adrenal hyperplasia, including contributions from a nurse, a physician and a patient.

UK endocrine nurses presented the Competency Framework for Adult Endocrine Nursing at the evening networking session. This generated much interest from nurses about its use in their own clinical practice. The evening closed with nursing posters and a buffet dinner at which nurses could socialise.

Many endocrine nurses felt it was important for us to meet, share our experiences and network during the ECE sessions. Consequently, we call on them all to participate in the nurse programme not only as attendees but also as speakers and chairs.

Importantly, a new Endocrine Nurses' Group has been formed within the European Society of Endocrinology (ESE), and we invite all our colleagues to join us. Our aim is to build up a network of endocrine nurses across Europe and internationally to share our experiences, benchmark practice and learn from one another.

PHILLIP YEOH
Endocrinology and Diabetes Manager/Specialist Nurse,
The London Clinic

Phillip Yeoh is a member of the ESE Nurses' Working Group.
For more information, visit ESE nurses at www.ese-hormones.org/nurse.

NIKKI KIEFFER NURSE COMMITTEE CHAIR

As I write this, I am looking forward to seeing you all at the Endocrine Nurse Update in Stratford-upon-Avon. I am sure that by the time you read this you will have enjoyed the packed programme and the chance to network with colleagues. Do let us have your feedback and tell us what you would like to see at future events.

I would like to thank Fiona for her interesting article on a one-stop thyroid lump clinic. It sounds an excellent service, and one to which we should all aspire. Thanks are also due to Phillip for his report on the European Congress of Endocrinology in Copenhagen. I was privileged to take part in this meeting, presenting the Society for Endocrinology's *Competency Framework for Adult Endocrine Nursing*, and I met several of our European colleagues. The Framework has generated a lot of interest from as far away as America and Australia, prompting closer collaboration with nurses from around the world. We hope to be working with them more closely in the future.

Please take advantage of the excellent leaflet from the Addison's Disease Self Help Group on the nursing care of patients with Addison's, to educate your ward colleagues and promote a safer environment for your patients.

Finally, please continue to tell us about your work. These pages for nurses are your opportunity to share information with your nursing colleagues, and to show everyone what a great job we do.

NIKKI KIEFFER

TEDct NURSE/HEALTH PROFESSIONAL BURSARY

The Thyroid Eye Disease Charitable Trust (TEDct) is excited to announce the launch of their new Nurse/Health Professional Bursary scheme. The bursaries can be used to support education (course fees) and/or for travel and accommodation expenses to attend such courses.

Applications for up to £500 are invited, though sums above £500 may also be considered. The course should be related to your work with patients who have thyroid eye disease, or be of benefit to your working practice with these patients. Further eligibility criteria and conditions of use apply, with details on the application forms.

Successful applicants will also present a session at a TEDct patient information meeting and write an article for the TEDct newsletter. For an application form and further details, contact TEDct, PO Box 1928, Bristol BS37 0AX (Tel: 0844-8008133; Email: ted@tedct.co.uk).

NEW VITAMIN D AND BONE HEALTH GUIDELINES

The Society for Endocrinology has endorsed the recently published guidelines entitled *Vitamin D and Bone Health: a Practical Clinical Guideline for Patient Management* from the National Osteoporosis Society. These provide best practice information on managing vitamin D deficiency in adults who have, or are at risk of developing, bone disease.

They have been developed by an expert group of clinicians and scientists following a review of published evidence and are designed to address three key areas:

- who to test for vitamin D deficiency
- how to interpret vitamin D measurements
- how to treat vitamin D deficiency

You can download your free copy at http://bit.ly/17GOw5d.

AN INTERVIEW WITH... CHRIS EDWARDS

INTERVIEWED BY MILES LEVY

I meet Chris Edwards at the Athenaeum Club in London, an institution specifically founded for those 'who enjoy the life of the mind'. As I enter the beautiful Georgian building, frequented by the likes of Dickens, Faraday and countless Nobel Prize winners, I feel a genuine sense of occasion. Chris Edwards greets me and makes me feel immediately at ease. He has a definite aura about him, yet is highly personable and youthful for his 71 years. He summons me up to the smoking room, and as we are served tea, I look at the gold-framed portraits that hang on the wood-panelled walls like an academic hall of fame. Chris Edwards recounts his story, and I soon realise that I am in the company of someone who could give them all a run for their money.

DESTINED FOR A MEDICAL CAREER

Chris Edwards is of good medical stock. His paternal grandfather, born in west Wales, was a successful GP in Middlesbrough, who qualified at Edinburgh in 1889. Following a trip to buy a car in London, Edwards' grandfather and great grandfather both became unconscious on the return journey. The chauffeur thought they were asleep but it took them 4 days to regain consciousness from this episode of carbon monoxide poisoning!

The family subsequently moved to London. Edwards' father qualified at Barts and became a consultant chest physician at St Albans and Welwyn Garden City Hospital. His mother was Sir Harold Gillies' theatre sister at Barts. Sir Harold was the father of plastic surgery. Assisting him was his distant cousin, the famous plastic surgeon-to-be, Sir Archie McIndoe.

Chris followed the family tradition to become a doctor. He went to Christ's College Cambridge and then Barts, qualifying with a distinction in medicine. He was soon spotted as a rising star, and got the professorial house job at Barts, having spent 6 months at Norfolk and Norwich, where he met his future wife, Sally.

EARLY CLINICAL PROMISE

Edwards was on the golden rotation – house physician at the Royal Brompton and the Hammersmith Hospital in 1968, working for Russell Fraser and Graham Joplin. On one of the first occasions he was on call, he saw a West Indian man who worked in the scrapyard near the hospital. He was writhing in abdominal agony. No one could work out what was wrong with him. Edwards wondered about lead poisoning from the scrapyard's batteries. He took a swab from his gums, and used an ion probe in a research lab upstairs to confirm high lead content. The patient improved with calcium gluconate, and when the case was presented at the infamous Hammersmith staff round, it was clear that a talented young physician had arrived on the scene.

LIFELONG BOND WITH CUTHBERT COPE

During another period on call, Cuthbert Cope, consultant physician and endocrinologist at the Hammersmith, was admitted with acute breathlessness. The Hammersmith consultants diagnosed atypical pneumonia, but Edwards was not convinced, as the chest X-ray was normal and Cope's jugular venous pressure was elevated.

At midnight, Cope deteriorated and Edwards arranged an electrocardiogram which showed an S1, Q3, T3 pattern, confirming his initial suspicion of a pulmonary embolus. He duly anti-coagulated Cope, bravely going against his seniors' advice, and Cope survived, remaining forever in Edwards' debt. The two became great friends and colleagues.

Edwards shared Cope's fascination with steroid metabolism, and became captivated by this aspect of physiology and medicine. Cope had written a book entitled *Adrenal Steroids and Disease*, which had a major influence on Edwards, who reflects, 'I have treasured this book over the years.'

DISCOVERY OF ALDOSTERONE

In 1951, Ian Bush pioneered a method allowing separation of steroids by paper chromatography. The husband and wife team of Jim Tait and Sylvia Simpson (they married in 1956) crystallised a steroid that retained sodium. They called it electrocortin. In 1954 they, working with Reichstein, published its chemical structure and, due to the aldehyde group at C18, they renamed it aldosterone. Chris Edwards comments, 'This aldehyde group was, unbeknown to me then, to be the key to my future. In particular the hemiacetal bridge between the 18-aldehyde group and the 11-hydroxyl group that protects aldosterone from metabolism by 11β-hydroxysteroid dehydrogenase.'

In 1954, Cuthbert Cope described an interesting patient with hypertension and hypokalaemia. The initial working diagnosis was a potassium-losing nephritis. Cope took a specimen of the patient's urine and found very large quantities of electrocortin. Unwittingly, Cope had beautifully described the syndrome that was to be formally described later that year by Jerry Conn; 'It could have been Cope's syndrome!'

CLINICAL AND RESEARCH LIFE AT BARTS

Edwards describes the remarkable endocrine clinic at Barts. Without the excellence of this early environmental influence, Edwards' path might have been very different. He is very appreciative of the role that Mike Besser played in his career as mentor, colleague and friend. Having published his first paper with Mike on the use of mithramycin in the treatment of malignant hypercalcaemia, he developed one of the first assays for the measurement of plasma and urinary arginine vasopressin (AVP). Tim Chard, Professor of Reproductive Medicine, used porous glass to extract tiny concentrations of oxytocin. Chard helped Edwards develop this technique to measure AVP.

Edwards graphically describes the horrifically painful investigation of pneumoencephalography for pituitary tumours, which led to publication of a series of reports on 37 (brave) patients. He also developed a thrombosis in his right arm when a catheter was put into his own petrosal sinus and infused with hypertonic saline for research on AVP!

Edwards and Besser published an interesting case of amenorrohoea, galactorrhoea and primary hypothyroidism. This syndrome had been described by Hennes in 1960, but the Barts' immunoassay technique refined the definition of the syndrome, demonstrating hyperprolactinaemia which normalised with thyroxine.

DOING THE ROUNDS IN THE USA

This was to come in particularly handy a few years later in 1972, when Edwards went to America and was invited to take the grand round at Harvard Medical School. By a remarkable co-incidence, Edwards was given a case of secondary amenorrhoea and galactorrhoea, thought by all the US professors to be a prolactinoma. Edwards broke tradition and asked if it was possible to see the patient.

As Edwards recalls, '[This was] clearly not a normal request! They brought her into the lecture theatre. On examination I found a firm goitre and delayed reflexes. I suggested that the most likely diagnosis was primary hypothyroidism and the syndrome that Hennes had first described. Gordon Williams' response was a very firm "I do not believe you". He suggested that blood was taken for the measurement of thyroxine and that we returned at 6pm for the result. You can imagine my relief when I turned out to be right!'

'Edwards broke tradition and asked if it was possible to see the patient.'

Whilst in the USA with Fred Bartter at NIH, Edwards became increasingly interested in the problem of low renin hypertension and the possibility that this might be associated with steroids other than aldosterone. He developed assays for the measurement of 18-OH-deoxycorticosterone and 18-OH-corticosterone. He also describes the political scandal of Nixon which captivated the nation at the time, and how the 'extraordinary' Dean hearings at the US Senate led to Nixon's eventual resignation in 1974.

Edwards returned from the USA in 1973 and spent a happy 7 years at Barts, becoming a senior lecturer in 1975. He developed an excellent direct assay for aldosterone, and was involved in seminal work on desmopressin and salt and water metabolism. He described a series of clinical cases with diabetes insipidus, diabetes mellitus, optic atrophy and deafness (known to a generation of future MRCP candidates as DIDMOAD, and now as Wolfram syndrome).

CONTINUED ON PAGE 22...

Christopher Edwards

CURRICULUM VITAE

Born: 12 February 1942, London, UK
Married to Sally, with three children

Education

1963	BA	University of Cambridge
1966	BChir	University of Cambridge
1966	MB	University of Cambridge
1967	MA	University of Cambridge
1974	MD	University of Cambridge

Affiliations, fellowships and awards

1968	Member of the Royal College of Physicians
1979	Fellow of the Royal College of Physicians
1981	Fellow of the Royal College of Physicians of Edinburgh
1990	Fellow of the Royal Society of Edinburgh
1998	Fellow of the Academy of Medical Sciences
2001	Honorary Doctor of Science, University of Aberdeen
2003	Fellow of Imperial College
2008	Honorary Doctor of Civil Law, Newcastle University
2008	Knight Bachelor

Previous appointments

1966	House Surgeon, Norfolk and Norwich Hospital
1967	House Physician, Medical Professorial Unit, St Bartholomew's Hospital
1968	House Physician, Brompton Hospital
1968	House Physician, Hammersmith Hospital
1969–1975	Lecturer in Medicine, St Bartholomew's Hospital
1972–1973	Peel Medical Research Trust Travelling Fellow, NIH, Bethesda, MD, USA
1975–1980	Senior Lecturer in Medicine and MRC Senior Research Fellow, St Bartholomew's Hospital
1975–1980	Honorary Consultant Physician
1980–1995	Moncrieff Arnott Professor of Clinical Medicine, University of Edinburgh
1981–1991	Chairman of the University Department of Medicine, Western General Hospital, Edinburgh
1991–1995	Dean of the Faculty of Medicine, University of Edinburgh
1992–1995	Provost, Faculty Group of Medicine and Veterinary Medicine
1995–2000	Principal, Imperial College School of Medicine
1995–2000	Professor of Medicine, University of London
2000–2007	Vice-Chancellor, Newcastle University
2008–2012	Chairman, Medical Education England

Present appointments

Chairman, Chelsea and Westminster Hospital NHS Foundation Trust
Senior Research Investigator, Experimental Physiology, Division of Medicine, Imperial College London
Chairman of Council, British Heart Foundation

AN INTERVIEW WITH... CHRIS EDWARDS

...CONTINUED FROM PAGE 21

CHAIR OF MEDICINE IN EDINBURGH

In 1980, he was rung by Joyce Baird, consultant diabetologist in Edinburgh, who asked, 'Have you seen the advert for the Chair of Medicine at the Western General Hospital?' Edwards was tempted, and asked his wife what she thought of the idea. She agreed, and with three young children in tow, they duly moved to Edinburgh for the next key phase of his career, Chair of Clinical Medicine in Edinburgh.

Chris inherited an excellent metabolic unit and brought two of his key laboratory staff with him, Brent Williams and Emad al Dujaili. Edwards was based at the Western General Hospital and was allocated one small laboratory and a seminar room. The latter proved to be unavailable. 'I spent the next few months doing a detailed audit of the academic space in my building at the Western. There was gross underuse and the Dean agreed that the space should be reallocated. It was the start of a quiet revolution.' This maximisation of an institution and turning it into a success became a recurrent theme in Edwards' career.

Edwards is clear that the key to any academic success is the appointment of talented individuals. One such person was a senior house officer from Birmingham who had qualified a few years earlier in Edinburgh. His name was Paul Stewart (now the UK's current leading opinion in all things related to the adrenal cortex). Another trainee specifically pointed out by Edwards is Jonathan Seckl.

THE PATIENT THAT CHANGED EVERYTHING

In August 1984, a 21-year-old man named Glynn was referred to Edwards at the Western General Hospital from Southampton. Glynn had a blood pressure of 200/145 mmHg, had lost vision in his left eye, and was grossly hypokalaemic with a serum potassium of 1.6 mmol/l, which had led to significant cardiac arrhythmias. He appeared to have hyperaldosteronism clinically, but the aldosterone level was at the lower limit of normal and did not rise on standing; the renin activity was low.

Maria New and Stanley Ulick from NIH had described a case of a 3-year-old American-Indian girl with hypertension and hypokalaemia which was presumed to be due to a hitherto unidentified steroid – they termed the condition apparent mineralocorticoid excess. Ulick showed a defect in the conversion of cortisol (the active metabolite) to cortisone (the inactive form), but no one knew how this defect might relate to hypertension.

CUSHING'S DISEASE OF THE KIDNEY

Edwards had a sudden burst of inspiration when driving on the M40 back to Edinburgh! For many years it was thought that there was only one enzyme involved in the metabolism of cortisol, 11β-hydroxysteroid dehydrogenase (11β-HSD), and that this was mainly in the liver. Carl Monder from the Population Council in New York had shown that there were actually two enzymes, one acting as an 11-dehydrogenase (converting cortisol to inactive cortisone), now termed 11β-HSD type 2, and the other an 11-reductase (converting cortisone to active cortisol), now known as 11β-HSD type 1.

Edwards' light bulb moment was to realise that Glynn's problem related to the enzyme in the kidney, and not the liver, the kidney being the key organ for the conversion of cortisol to inactive cortisone and the liver the main site for the conversion of cortisone to active cortisol.

The hypothesis was that, in Glynn, there was an inability to inactivate cortisol to cortisone due to a presumed defect in the enzyme 11β-HSD (now known as type 2) in the kidney. The mineralocorticoid receptor (MR) had recently been cloned by Arriza and shown to be non-specific, binding cortisol and aldosterone with equal affinity. Edwards suggested that the MR might normally be protected by its adjacency to the enzyme 11β-HSD, so that it in normal subjects it never 'saw' cortisol and hence was aldosterone-specific. He proposed that the absence of this protective mechanism in Glynn resulted in cortisol acting as a mineralocorticoid that then produced gross sodium retention, potassium loss and hypertension.

Glynn's urine was sent to Cedric Shackleton, an excellent steroid chemist in the USA, to look at the ratio of cortisol to cortisone metabolites (usually 1.3). The ratio in Glynn was 13.5, more than ten times the normal value, so confirming Edwards' diagnosis.

"The problem with very rare conditions is just that – they are rare. We needed a model system in which to test our ideas."

Subsequently, through work in the Edinburgh laboratory, John Corrie synthesised 11α-[^{3}H]cortisol and showed that normal subjects converted this to cortisone and tritiated water, but Glynn could not do this. More remarkably, giving dexamethasone to Glynn, which inhibited adrenocorticotrophin and therefore cortisol, led to a normalisation of his blood pressure and potassium, and this was immediately reversed with cortisol infusion. It all fitted. Stewart and Edwards published the case as an abstract in 1985 entitled 'Cushing's disease of the kidney'.[1]

THE LIQUORICE CONNECTION

'The problem with very rare conditions is just that – they are rare. We needed a model system in which to test our ideas.' Edwards and Stewart recognised the remarkable parallel between this case and an observation initially made by a Dutch pharmacist in 1946 that people taking liquorice for peptic ulcers developed hypertension and hypokalaemia. They went on to show that the active component of liquorice, glycyrrhetinic acid, was a potent inhibitor of 11β-HSD. Stewart published this in *The Lancet* in 1987 as 'Mineralocorticoid activity of liquorice: 11β-HSD comes of age'.[2]

Edwards then tells the story of how he was let down by a potential research collaborative group in Australia. He is genuinely upset by this, and feels that 'Many years on it is perhaps worth recounting what actually happened.'

The Australian group had shown in 1983 that the same steroid-binding species could be occupied by a mineralocorticoid in the kidney and a glucocorticoid in the hippocampus. Edwards wrote to the lead researcher and suggested that the answer to the conundrum must be the presence of 11β-HSD in the kidney. He proposed a research collaboration and sent a preprint of their *Lancet* liquorice paper. A collaborative project was agreed, the group did the experiments that Edwards suggested and confirmed his idea was correct. They then published the results without including Edwards' group, and suggested that they would have done the experiments anyway after Stewart's *Lancet* paper had come out. 'I was gutted that a senior scientist could behave in such as way. I had a more idealistic view of international scientific collaboration in those days.'

Chelsea and Westminster Hospital

Edwards' group published their own series of experiments in *The Lancet* in 1988,[3] and since this seminal work on 11β-HSD, more than 2,000 publications and 55 patents have been filed in this area, validating Edwards' fundamental contribution to endocrinology.

MANY LEADING ROLES

Chris Edwards has repeatedly been invited to take leadership of major medical and academic institutions. In 1991, he was elected to become Dean of the Faculty of Medicine in Edinburgh. The University was bankrupt and he oversaw a major restructuring so that medicine and veterinary medicine were joined. Both faculties flourished and grew under his clear vision. There is not enough space here to recount the finer details of all Edwards' achievements, but time and again he has demonstrated amazing clarity of vision and a knack for successfully restructuring institutions on a large scale. He is keen to point out that all his successes have been collaborative, particularly emphasising the role of his outstanding administrators.

In 1995, he was invited by Sir Ron Oxburgh, Rector of Imperial College, to become the first Principal of the Imperial College School of Medicine and oversee the merger between the Royal Postgraduate Medical School at the Hammersmith, the Charing Cross and Westminster Medical School, the National Heart and Lung Institute at the Brompton and St Mary's Hospital Medical School to form the new medical school. Not surprisingly this met with much resistance initially. After two Acts of Parliament, and much persuading of inflexible senior clinical academics, he successfully oversaw the merger, securing funding for the construction of major medical research sites. Imperial's medical research grant income increased from £66 million to £100 million in 3 years, over 50% of the entire College grant income.

In 2000, Edwards was appointed as Vice Chancellor of Newcastle University. Once again, Edwards could see that the University had 'lost its way'. Soon after arriving at Newcastle, he went to a neurophysiology lecture on sophisticated software that could test interconnections of the mouse visual and motor systems. The next day, Edwards visited the surprised Professor of Neuroscience who had given the lecture, asking if he could use his software to examine key connections in the University. Using this innovative application of technology and other approaches, he made wholesale structural changes. He also introduced a voluntary redundancy scheme that freed up funding and allowed the University to make a major investment in its areas of strength. This restructuring was not universally popular. It caused the head of the local branch of the Association of University Teachers to nickname Edwards 'Chainsaw'. As a result of Edwards' changes, the University grew in stature, its total annual income rising from £160 million to £324 million during his tenure. The headline in the local press towards the end of this period was 'Chainsaw restores the cutting edge'.

WHAT NOW AND WHAT NEXT?

The amount that Chris Edwards has achieved in his working life is incredible, and he is showing no signs of slowing down. He is currently Chairman of Chelsea and Westminster Hospital NHS Foundation Trust, Chairman of Council of the British Heart Foundation, and Senior Research Investigator at Imperial. Amongst other pursuits, he has set up a successful drug discovery company (Argenta), a deep geothermal energy venture (Cluff Geothermal), which he hopes may help to produce low carbon energy in the north east of England and Africa, and is on the board of the Planet Earth Institute, which aims to bring 21st century science to Africa by funding 100 PhD studentships between Africa and the UK.

Towards the end of our meeting, with a smile, he shows me his hands, telling me he has been diagnosed with rheumatoid arthritis. I tell him they look very un-rheumatoid arthritis-like, and he tells me how his own treatment regime of a low dose of dexamethasone at night could be the reason his hands have not undergone rheumatoid change. He has concluded that one factor in the pathophysiology of rheumatoid arthritis, and a number of other chronic inflammatory diseases, is relative nocturnal cortisol deficiency, due to tumour necrosis factor enhancing expression of 11β -HSD type 1, and I start to think how this might explain the early morning stiffness of rheumatological conditions (Edwards has recently published these thoughts in *Journal of Clinical Endocrinology and Metabolism*[4]).

'I think of Chris Edwards as ... a shining example of why our country is still seen as one that punches above its weight.'

Like other interviews I have done, I come to the conclusion that you cannot stop someone coming up with good ideas. Like other high calibre physicians, Edwards would have excelled at any branch of medicine.

Edwards was awarded a knighthood in 2008 for services to higher education, medical science and regeneration in the north east of England, which restores some of my faith in the honours system. I think of Chris Edwards as someone who sees the bigger picture. His key research ideas were based on basic clinical observation, which I think is the best starting place for clinical research. He is excellent company, has a whiff of Britain's colonial past, and is surely a shining example of why our country is still seen as one that punches above its weight.

Most importantly, Edwards has a genuine interest in people and communities, and strives to improve things for those less fortunate than himself. After 4 hours of non-stop chat, he leaves me with this; 'Endocrinology is an infectious disease that I caught many years ago. Fortunately there is no cure.' I can confirm that Chris Edwards is showing absolutely no signs of entering remission.

MILES LEVY
EDITOR, THE ENDOCRINOLOGIST

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HOW TO GET YOUR WORK PUBLISHED: A GUIDE TO WRITING YOUR RESEARCH PAPER

WRITTEN BY ADRIAN JL CLARK

There is little point in conducting research unless you can tell others about it. You need to show you can disseminate your discoveries to many people: the interview panel for your next job, your Head of Department, the funding bodies who pay your salary and even your Grandma. But, fundamentally, you need to make the results available.

Normally you will do this by publishing your work in a peer-reviewed scientific journal. The 'better' the journal, the better it reflects on your ability. So, the question is, 'How do I maximise my chances of getting published in a good journal?'

PLAN AHEAD

It is a poor idea to think that you should perform your research project, see what the data look like, and only then consider how to publish. Instead, it is a good idea to be continuously thinking about how you can portray your findings as your project progresses. Most research departments will facilitate this by asking you to present intermittent updates of your work. This approach will allow you to see flaws in your strategy early on, rather than when you come to write it up. Take note of the criticisms of your colleagues at this stage, even if you think they are dumb. The reviewers may have similar misconceptions.

Often there is more than one way to present a body of work. Does this come across better as a single major paper or several smaller papers? Sometimes it is useful to have your initial premise published prior to the important follow up. There is no universal answer to this, except don't 'salami slice' your data. It may give you more papers, but their quality and minimal content will be noted. Furthermore, there is no guarantee that the second and subsequent slices of work will get published.

CHOOSE YOUR TARGET JOURNAL

We all want to get our work published in the 'best' journal we can, but we need to be realistic. Not every paper is a *Nature*, *Cell* or *Science* publication. It is really important to choose the journal that is appropriate for your work.

If your findings have significant implications beyond the focused area in which you work, then go for a general journal. If not, select a specialist journal. Often you will receive a better quality, more expert and constructively helpful review from a specialist journal. Look at the areas of interest for each contender journal carefully. Then look at what else they've published this year. Every week we reject papers without review from *Journal of Endocrinology* simply because the authors haven't checked the remit of the journal.

1. Think about how you can portray your findings as your project progresses. Don't leave it until you have gathered all your data.

2. Choose the journal that is appropriate for your work.

3. Decide what the message of your paper is to be. What data do you need to show this conclusively?

4. State your hypothesis clearly. Editors, reviewers and readers love it if you are clear what you are asking.

5. Don't be coy about recognising your work's shortcomings. If you don't, the reviewers will make sure you know it soon enough!

6. Take note of others' comments – if your readers don't understand something, it's probably because you haven't made it clear.

CONSTRUCT YOUR PAPER

Writing a scientific paper is a skilled business. It would be wrong to generalise about how to do this, but as a rule of thumb I suggest that you decide what the message of your paper is to be. What data do you need to show this conclusively? Often you can think of this as figures and tables, and collect this information together before you start to write. Have you got all your controls? Don't include irrelevant data, even if it took you 6 months to collect.

Write your **introduction**. Make it concise but complete. Provide relevant background information, but DON'T write a mini-review of the subject. Lead up to your hypothesis and state this clearly. Editors, reviewers and readers love it if you are clear what question you are asking.

Write the **results** section in such a way that each piece of data leads to the next, referring to the figures or tables, and telling a story as you go. Don't discuss the meaning of the results in this section unless it is essential to understand why you did the next experiment. Unless the journal you are writing for requests that results and discussion should be combined, leave discussion to the next section.

Before you write your **discussion**, write down each of the key points you need to make. Each of these points will become a paragraph (or less). Start by summarising your results and point out their meaning and their pitfalls. Don't be coy about recognising shortcomings. If you don't, the reviewers will make sure you know it soon enough! Now, expand your discussion to point out the finding's wider importance. Don't write a review of the area, but cite appropriate reviews if need be. Don't criticise others work, even if it was rubbish – they may be your reviewers! A final summary sentence or two often hammers home your discovery very effectively.

The **material and methods** section can be tedious to write, but is really vital to convince the sceptical researcher on the other side of the world, enabling them to reproduce your experiments and prove to themselves that you are right. Much of your methodology will be standard and original descriptive papers can be cited – but make sure your version of the technique isn't a modification of the original. If it is, say how it differs. Use an online supplement for bulky data descriptions if need be. Say where you obtained samples and reagents. Don't forget to describe the ethical permissions and approvals.

Use **citations and references** wisely. Cite accessible papers, not book chapters, abstracts or obscure non-English texts. Read the papers you refer to and make sure they say what you think they do. Check that your reference list and citation style is uniform and appropriate for the journal. Whilst this can be changed easily enough, it shouts laziness in your preparation if it is wrong.

Work on the **figures**. There are excellent professional quality software packages widely available now which allow you to make impressive images and graphs. Apart from making your work more understandable and persuasive, it lends a professional air to the manuscript that will influence reviewers in your favour. Make sure that image resolution is high, and take careful note of guidelines on presentation of blot and gel image data. You may be asked by reviewers to provide original images for these.

Finally, write the **abstract and title**. The title should be short and to the point. Some journals have length limits on titles. The title is what will capture the attention of the scientist scanning a table of contents. If this doesn't capture him or her, little else will. The abstract needs to summarise everything in the paper and will be the next key source of information. Even in your own research area, the majority will not read beyond this.

WHAT NEXT?

Now you have written your paper, don't submit it! Your co-authors need to read it and agree to it. They may require substantial changes, but at the end of the day they will have to share the responsibility for its content with you. Get others to read it. Re-read it yourself again and again. Adjust and refine it. Take note of others' comments – your reviewers may have the same thoughts. If your readers don't understand some aspect, it's probably because you haven't made it clear, not that they are thick!

Finally, you should be ready to submit.

ADRIAN JL CLARK
Editor-in-Chief, Journal of Endocrinology and Journal of Molecular Endocrinology

Adrian Clark is Dean of Research and Deputy Principal at St George's University of London and was formerly Professor of Medicine and Head of Academic Endocrinology at Barts & the London.

THE LEGACY OF LIFE... REMEMBERING PROFESSOR SIR ROBERT EDWARDS (1925–2013)

WRITTEN BY HOWARD JACOBS

Professor Sir Robert Edwards MA, Hon ScD, CBE, FRS died after a long and debilitating illness in April of this year. Despite his numerous accomplishments, matched only by his immense erudition, Professor Edwards, known to friends and colleagues as Bob, was generally shunned by the Establishment for most of his life.

His extensive contributions to biological science and to healthcare were eventually acknowledged by the award of the Nobel Prize in Physiology or Medicine in 2010 and of a knighthood in the following year. Sadly, however, bestowal of these honours was deferred beyond the time that Bob was well enough to take much pleasure in them. That delay was a disgrace.

If ever a person exemplified Kipling's admonishment: '...meet with Triumph and Disaster, And treat those two impostors just the same' it must be Bob Edwards.

Everyone knows that Bob Edwards, together with the late Patrick Steptoe, invented *in vitro* fertilisation (IVF) as a treatment for human infertility. Many may have forgotten that their first 'test-tube baby' was born as long as 35 years ago and that, since then, more than 5 million babies have been born as a result of IVF. The achievement is all the more astounding when we remember that these children were born into infertile families for whom alternative treatments were few and, for the most part, ineffective.

Professor Martin Johnson, a former research student of Bob's, has published a scholarly historical account of the science, and the politics of the science, that led to the success of Edwards and Steptoe's project.[1] He has also described how the two of them faced obstacles that would have deterred a less determined pair, how they were given no financial support from UK funding bodies,[2] and how they were regularly attacked, not only by religious leaders and the press, but also by most of their scientific and clinical colleagues. Johnson has described how, as a graduate student, he was ostracised at meetings and in the departmental tea room because of his association with Bob.[3]

The contributions to biological science made by Professor Edwards and his colleagues include the demonstration in the 1960s of the viability of preimplantation genetic diagnosis in an animal model and the isolation of stem cells from early rabbit embryos. Many more scientific advances emerged from his laboratory, for details of which the interested reader is referred to the review by Gardner & Johnson.[4]

Bob Edwards realised the societal implications of his work, and wrote and talked extensively on the subject of reproductive ethics. He was committed to public and reliable dissemination of science at a time when scientists were supposed to remain in the laboratory and speak of their work only to other scientists – hardly imaginable nowadays when establishing 'impact' is such a crucial feature of a Research Excellence Framework submission. In those days, such openness attracted severe criticism from colleagues and, most importantly, from those within the funding agencies.

Bob Edwards was a founding member and major instigator of the European Society for Human Reproduction and Embryology and the first editor of its journal, *Human Reproduction,* which subsequently gave birth to *Human Reproduction Update* and *Molecular Human Reproduction.*

Finally, on a personal note, I want to mention that, in addition to the excellence of his science, his central role in changing attitudes to reproductive medicine and his stunning accomplishments, there is the memory of Edwards-the-man. Bob was committed, socially very aware and active (he had been a Labour councillor for 5 years); he had a generous disposition and was always open to discussion. Like many others, I know it was a privilege to have known him, and my admiration steadily increases the more about him is published. I fear I shall not look upon his like again.

HOWARD JACOBS

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PASIREOTIDE: THE LONG ROAD TO CUSHING'S TREATMENT

WRITTEN BY PAUL FOSTER

Welcome to our new regular feature 'From bench to bedside', where we take a more in-depth look at the world of drug development and chart the history, progress and potential future of endocrine drugs.

The diagnosis and treatment of Cushing's disease, defined as the over-secretion of adrenocorticotrophin (ACTH) from the pituitary, have had a chequered history.

When Harvey Cushing, an outstanding surgeon and Moseley Professor of Surgery at Harvard School of Medicine, identified the condition in his 1932 paper on a patient with a 'polyglandular syndrome', it would have been hard to believe that it would take almost a century to develop the first approved pharmacological agent for its treatment.

But, late last year, after priority review and orphan drug designation, the US Food and Drug Administration (FDA) approved the Novartis-developed pasireotide (SOM230, trade name Signifor), for the treatment of Cushing's disease. Pasireotide is a somatostatin analogue with a 40-fold increased affinity for somatostatin receptor 5 (sstr5) compared with other known somatostatin mimetics. However, the road towards pasireotide's development has been long, and represents a paradigm of the necessary studies required to drive a compound towards clinical acceptance.

SUCCESSOR TO OCTREOTIDE

Typically, the use of somatostatin analogues is the standard for patients with acromegaly or symptoms of neuroendocrine tumours (NETs). For years, the biochemistry of these conditions has been controlled by octreotide (Sandostatin), first synthesised in 1979 and effective in around 65% of acromegaly patients. Most patients with symptomatic carcinoid tumours initially respond to octreotide treatment. Therefore, in about 35% of acromegaly patients octreotide fails and long term treatment can cause tachyphylaxis. Importantly, in the early 1990s, studies demonstrated that octreotide, which mainly activates somatostatin receptor 2 (sstr2), and to a lesser extend sstr5, does not affect ACTH levels in patients with Cushing's disease.

Consequently, Novartis, who had developed octreotide during the 1980s, realised that a somatostatin analogue with a multi-receptor binding profile would have the potential to be effective not only in patients with acromegaly or carcinoid tumours, but also in other diseases associated with somatostatin receptor expression other than sstr2.

Enter pasireotide, a somatostatin analogue which was shown in 2002 to have a high binding affinity for somatostatin receptor subtypes sstr1, -2, -3 and -5. Compared with octreotide, the functional activities of pasireotide on sstr1, sstr3 and sstr5 were >30-, 11- and 158-fold higher respectively.

But why use a synthetic compound when endogenous somatostatin already binds to these receptors? The problem lies with somatostatin's very short plasma half-life (<3min), making it therapeutically limited. In contrast, pasireotide, due to its cyclohexapeptide structure, is metabolically stable, with a plasma half-life of 12h.

SUPPRESSION OF ACTH

Further work confirmed that most human corticotroph adenomas express multiple somatostatin receptors, dominated by sstr5, and that sstr2 and sstr5 regulate ACTH secretion in corticotroph tumour cell lines. In 2002, pasireotide was shown to inhibit ACTH secretion from these cell lines, and suppressed ACTH secretion in rats by 45%. Consequently, these basic functional *in vitro* and *in vivo* results indicated pasireotide's potential to regulate plasma ACTH in patients with persistent or recurrent Cushing's disease.

Subsequent clinical trials of pasireotide in adults with ACTH-dependent Cushing's disease showed promise. The FDA's announcement late last year follows a recent year-long double-blind phase III trial where 162 patients were treated with either 2x600µg or 2x900µg pasireotide s.c. daily. Treatment effect was checked by measuring urinary free cortisol (UFC) value after 6 months' administration, during which time the mean reduction was 47.9%, accompanied by amelioration of clinical symptoms such as blood pressure, cholesterol value and weight loss.

Although those success rates were relatively low, nearly 60% of 103 patients for whom baseline and 6-month UFC levels were available showed cortisol reductions of at least 50%. However, nearly three-quarters of the participants experienced hyperglycemia-related adverse events: 6% left the study and 46% required a new glucose-lowering medication. Despite this, pasireotide approval is a significant step in management of Cushing's disease.

WHAT NEXT FOR PASIREOTIDE?

Interestingly, this is not the end of pasireotide's story. There is hope it will be effective at treating multiple endocrine neoplasia 1 (MEN1). Recent studies using a transgenic mouse model of MEN1 insulinoma showed it reduced tumour growth by several measures, potentially clearing the way for human trials in MEN1 where surgical resection of the insulinoma is not possible or metastases are evident. Indeed, in a phase II study, pasireotide has now shown efficacy in advanced NETs refractory or resistant to octreotide.

The bench-to-bedside development of pasireotide is clearly a success story; the length of time required for its approval represents the norm for many drugs. From a hypothesis in the 1980s followed by pasireotide's synthesis in the late 1990s, initial *in vitro* and *in vivo* studies in the early 2000s, and first clinical trial in 2005 onwards, this concludes at least 25 years of scientific effort. And, it is not over. Understanding pasireotide's efficacy in other endocrine conditions is in its infancy, with many more trials for this drug in the future.

PAUL FOSTER
Lecturer in Molecular Endocrinology,
University of Birmingham

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KISSPEPTINS: REACHING THE HEART OF REPRODUCTION

WRITTEN BY WALJIT DHILLO & SHAKUNTHALA NARAYANASWAMY

Kisspeptins are neuropeptides encoded by the KISS-1 gene. This gene was discovered in 1996 in Hershey, PA, USA, and was subsequently named after the famous chocolates called Hershey's Kisses.

The KISS-1 gene was thought to have a role in suppressing tumour metastasis in melanoma cells, since the gene was up-regulated in melanoma cells that had lost their potential to metastasise. In 1999, the kisspeptin receptor (KISS1R) was identified (previously known as the orphan G protein-coupled receptor 54 or GPR54).

The peptide product of the KISS-1 gene is a 145 amino acid peptide which is cleaved into shorter peptides of kisspeptin-54, -14, -13 and -10 (denoting their numbers of amino acids). All these isoforms have been shown to have agonist activity at the receptor (KISS1R) and are collectively referred to as kisspeptins.

AN ENDOCRINE ROLE

The importance of kisspeptin in endocrinology was only established in 2003. It was shown that people with inactivating mutations of the KISS1R failed to go through puberty due to isolated hypogonadotrophic hypogonadism. KISS1R-deficient mice had an identical phenotype. Conversely, it was later shown that activating mutations of KISS1R in humans results in central precocious puberty. Therefore, kisspeptin has a fundamental role in the onset of puberty and thus subsequent fertility – perhaps this is the biological basis of why we all remember our first kiss.

Extensive studies have detailed the effects of kisspeptin on reproductive hormone release in almost all species studied to date. Acute and intermittent repeated administration of kisspeptin powerfully stimulates gonadotrophin release. Chronic administration of high doses of kisspeptin can result in an acute stimulation followed by desensitisation of the KISS1R. It appears that the effects of kisspeptin are predominantly mediated through stimulation of the release of gonadotrophin-releasing hormone (GnRH), since pre-administration of a GnRH antagonist blocks the effects of kisspeptin. Kisspeptin expression is also sensitive to oestrogen and testosterone feedback. It has a potential role in seasonal regulation of reproductive activity in seasonal breeders. Increasing evidence suggests that kisspeptin may serve as a metabolic link between nutrition and reproductive function.

CLINICAL STUDIES

Recent studies have investigated the effects of kisspeptin administration to healthy human volunteers. In males it causes a potent rise in gonadotrophins with no side effects. In women with regular menstrual cycles it also stimulates gonadotrophin release, but has its greatest effect in the pre-ovulatory phase of the cycle. Women with hypothalamic amenorrhoea were extremely responsive to kisspeptin administration, and showed a four times greater luteinising hormone (LH) response than was seen in healthy females in the follicular phase.

KISSPEPTIN – KEY FACTS

1. Kisspeptin is vital for puberty – loss of function mutations lead to hypogonadotrophic hypogonadism, while activating mutations cause precocious puberty
2. Hypothalamic GnRH release is stimulated by kisspeptin, so increasing gonadotrophin levels
3. Kisspeptin administration powerfully stimulates LH release and may increase LH pulsatility
4. Prolonged high dose kisspeptin administration can cause desensitisation and lower gonadotrophins

Kisspeptin offers exciting therapeutic potential. The acute administration of kisspeptin to increase reproductive hormone release by stimulating GnRH could represent a more natural pattern of hormone release in infertility. For example, current studies in women are underway to determine whether kisspeptin can be used to lower the risk of ovarian hyperstimulation syndrome during *in vitro* fertilisation therapy. Recent data in humans also suggest that administration of kisspeptin may be able to stimulate LH pulsatility, which raises important potential therapeutic possibilities for the treatment of women with anovulatory infertility.

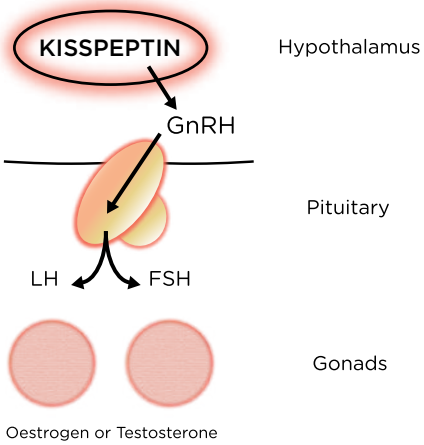
The phenomenon of prolonged high dose kisspeptin administration causing desensitisation (and kisspeptin's potential anti-metastatic role) suggests that it could be utilised in the future to treat hormone-sensitive cancers. Long-acting forms of kisspeptin are being developed currently with promising early results in humans.

Watch this space – we think kiss is here to stay!

WALJIT DHILLO & SHAKUNTHALA NARAYANASWAMY

Waljit Dhillo is Professor of Endocrinology and Metabolism at Imperial College London. He is funded by an NIHR Career Development Fellowship and was awarded the Royal College of Physicians Goulstonian Lectureship for his research on kisspeptin.

Shakunthala Narayanaswamy is an NIHR Academic Clinical Fellow and Specialist Registrar in Diabetes and Endocrinology at Imperial College London.



Kisspeptin acts mainly via hypothalamic GnRH release, with some possible direct effect on the pituitary and gonads.

IN THE NEWS...

A clinical trial run by Hammersmith Hospital and Imperial College London has led to the birth earlier this year of the first baby to result from the use of kisspeptin to stimulate egg release.

Read more at **http://bbc.in/12uDddb.**

JOE/JME PRIZE WINNER: ENHANCING RADIOIODINE UPTAKE IN THYROID CANCER

WRITTEN BY VICKI SMITH

Vicki Smith recently won the 2013 JOE/JME Prize, awarded this year by Journal of Molecular Endocrinology. Here, she summarises her studies on novel methods to enhance efficiency in ablative radioiodine therapy for thyroid cancer.

Ablative radioiodine therapy is critical to the treatment of differentiated thyroid cancers and their metastases, and relies on the innate ability of thyroid cells to take up iodide via the sodium iodide symporter (NIS). Tumours with reduced avidity for radioiodine have a poorer prognosis, and current research seeks to identify ways to induce NIS activity and hence radioiodine uptake. This can be achieved either through the induction of endogenous NIS or via targeted NIS gene therapy, and has opened up the possibility of using radioiodine to treat non-thyroidal cancers, such as breast and prostate cancer.

Pituitary tumour-transforming gene binding factor (PBF) is a transmembrane glycoprotein that is significantly overexpressed in thyroid cancer. High levels of PBF expression are associated with early tumour recurrence and decreased survival rate. Functionally, we have shown that PBF can repress iodide uptake, and my research has focused on investigating the mechanism behind this.

HOW DOES PBF REPRESS NIS?

PBF overexpression significantly reduces NIS expression *in vitro*. Across a series of experiments we have determined that PBF has no effect on the basal NIS promoter but significantly represses an enhancer element (located around 9kb upstream of the human NIS gene) that is critical for thyrotrophin (TSH)-induced NIS expression.

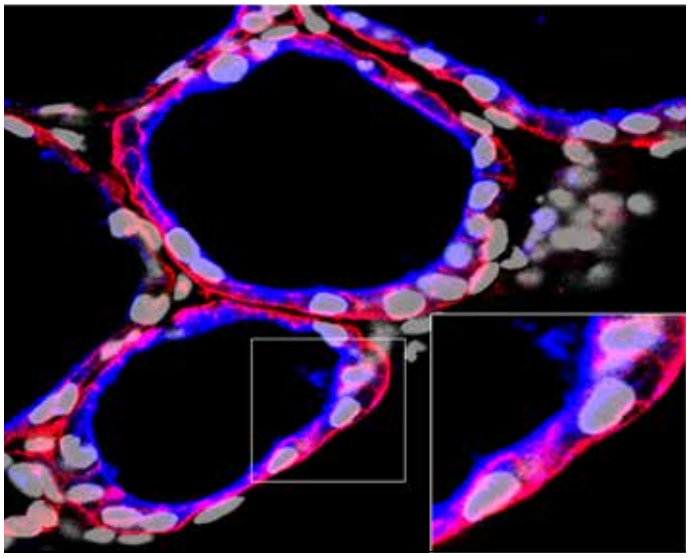
Binding assays *in vitro* confirmed an interaction between NIS and PBF, with immunofluorescent studies demonstrating colocalisation between NIS and PBF, predominantly within intracellular vesicles. Intracellular colocalisation was also evident in a panel of ten cancer cell lines. Importantly, PBF overexpression was associated with a significant reduction in NIS localisation at the plasma membrane.

We went on to pursue these findings in our mouse model of thyroid-specific PBF overexpression. Primary thyroid cultures derived from these mice demonstrated significantly reduced iodide uptake and, crucially, this phenotype could be rescued by downregulating PBF expression.

Overall, these studies suggested that PBF can bind NIS and modulate its localisation, impacting on iodide uptake and representing a novel mechanism of NIS repression. As PBF is overexpressed in a number of cancers, this may have implications for the use of radioiodine treatment in multiple tumour types.

REGULATION OF THYROID HORMONE SECRETION

Because our data clearly showed that PBF is able to bind to and internalise cell surface transporters such as NIS, we investigated whether PBF could similarly influence monocarboxylate transporter 8 (MCT8), the transporter that mediates thyroid hormone secretion from the thyroid gland. Indeed, PBF bound to MCT8 *in vitro*, and overexpression of PBF resulted in the internalisation of MCT8. *In vivo*, colocalisation between PBF and MCT8 was evident in the thyroid glands of the PBF transgenic mice, which contained significantly increased levels of thyroid hormone. Impaired thyroid hormone secretion was determined by TSH stimulation assays, suggesting that PBF may have a role in the overall regulation of thyroid hormone biosynthesis and secretion.



Pituitary tumour-transforming gene binding factor (PBF; blue) and monocarboxylate transporter 8 (MCT8; red) in the thyroid of the PBF transgenic mouse.

THERAPEUTIC POTENTIAL

Most recently, my studies have focused on trying to overcome PBF repression of NIS. The C-terminal of PBF contains an endocytosis motif. Mutation of the critical tyrosine residue (Y174) contained within this motif results in a significant accumulation of PBF at the plasma membrane, and almost completely abrogates the interaction between PBF and NIS.

PBF-Y174 undergoes phosphorylation, with Src being the putative tyrosine kinase that undertakes this role. Src overexpression significantly increases PBF phosphorylation, while Src inhibition potently represses PBF-Y174 phosphorylation, both in papillary thyroid carcinoma thyroid lines such as TPC1 and K1 and in human primary thyroid cultures. Importantly, Src inhibition entirely overcame PBF repression of iodide uptake, which is of direct clinical importance to the treatment of thyroid cancer.

We believe that the phosphorylation of PBF-Y174 is involved in the binding and internalisation of NIS, and therefore propose that, through the inhibition of PBF phosphorylation, NIS repression can be prevented and iodide uptake restored. Hence, targeting PBF phosphorylation at residue Y174 via tyrosine kinase inhibitors may be a novel therapeutic strategy to enhance the efficacy of ablative radioiodine treatment in thyroid and other tumours.

VICKI SMITH
Research Fellow, University of Birmingham

Dr Vicki Smith graduated in medical biochemistry from the University of Leicester, before spending 4 years at a biopharmaceutical company. She completed her PhD at the University of Birmingham under the supervision of Professors Chris McCabe and Jayne Franklyn and now works there as a post-doctoral research fellow funded by the Medical Research Council.

PRIORITISING PITUITARY PATIENTS: THE PITUITARY FOUNDATION

WRITTEN BY STEPHANIE BALDEWEG

For almost 10 years, I have been a Trustee on the Board of The Pituitary Foundation. I am delighted both to finally get this chance to write (a lifelong dream) and to have the opportunity to promote this charity, as it is close to my heart.

It is estimated that there are approximately 70,000 people with a pituitary condition in the UK. To meet the need for information and support, The Pituitary Foundation was set up in 1994 and was registered as a charity shortly afterwards. There were a small number of founders (many names will be familiar to you) including Professor Stafford Lightman, Professor John Wass, Gail Weingartner, Sue Thorn and Ann Bailey. Today there is a team of 7 staff and over 100 dedicated volunteers.

WHAT DO THE PATIENTS THINK?

When mentioning The Pituitary Foundation to patients, the response is almost unanimously enthusiastic. The stories told go from help for the newly diagnosed patient to support throughout the lifelong pituitary journey. Patients relate how they use the helpline (almost 700 calls in 2012), email support (over a 1,000 emails in 2012) and get support and advice from the endocrine nurse (almost 300 direct contacts last year).

> "A year ago, I made that first call to you, which gave me the confidence and the will to fight back and demand the care that my child really needed."

Patients marvel about the stories and information in *Pituitary Life* magazine, which we produce three times per year. Each edition is read by more than 5,000 people connected with pituitary conditions.

Many patients attend our local support groups for peer support and education, and travel to the national pituitary conferences. The last conference, in Birmingham in April 2013, attracted almost 200 delegates.

> "Just wanted to drop a line to say thank you once again, and also express my gratitude for all the help and support you gave me. It really had a lasting effect."

WHAT ABOUT ENDOCRINOLOGISTS?

When mentioning The Pituitary Foundation to colleagues, the response seems more mixed. One group strongly supports The Foundation. Dr John Newell-Price and I are both Trustees. There is a very active medical committee of endocrinologists, neurosurgeons, nurse specialists and psychologists, forming a giant pituitary multidisciplinary team, many of whom you will be familiar with. We are also aware of the large group of endocrinologists who are supportive of The Foundation and put their patients in touch with its services.

The other group, which I am hoping to reduce with this article, seems unaware of what The Pituitary Foundation can offer. If you have read to here, you have automatically upgraded...

WHAT CAN YOU DO FOR THE PITUITARY FOUNDATION?

Put your patients in touch with The Foundation. We can supply free A5 'referral pads', which include single tear-off leaflets for patients, giving comprehensive information about our patient support and information services. You can also run open days, lecture at The Foundation's events or fundraise. To obtain information from The Pituitary Foundation, or to offer your support or services, contact 0845 450 0376 or enquiries@pituitary.org.uk.

WHAT CAN THE FOUNDATION DO FOR YOU?

The Pituitary Foundation endeavours to create awareness about pituitary conditions and the challenges that patients face. It provides support to patients over and above what is offered by the NHS, with comprehensive written material about most pituitary conditions, such as hydrocortisone emergency rules and a holiday checklist. There is even a hydrocortisone 'app' for smartphones.

We have launched a new website (www.pituitary.org.uk), offering all the material online. You can befriend us on Facebook (www.facebook.com/pituitaryfoundation) or follow us on Twitter @Pituitary_org.

So, if you are already a supporter of The Pituitary Foundation I hope you agree with my thoughts. If this is new to you, I hope that I have managed to intrigue you.

STEPHANIE BALDEWEG
Trustee, The Pituitary Foundation

Stephanie Baldeweg is Consultant Endocrinologist at the University College London Hospitals and National Hospital for Neurology and Neurosurgery.

> "I was very pleased to have got in touch with your helpline. It is so reassuring to know there are people on the end of the phone that understand what people with a rare illness are talking about. I would certainly recommend anyone with pituitary problems to support The Pituitary Foundation, as they do a marvellous job of informing people about pituitary problems."

iCORTISOL

This new app from The Pituitary Foundation provides a quick reference guide for patients who take hydrocortisone. Simple to use, it includes features such as a smart reminder system, a dose logging system, quick reference information about sick day rules and what to do in an emergency situation. iCortisol is suitable for any Apple device, and patients can download it for £1.99 from the App Store (70p will be donated to The Pituitary Foundation).

CONTACT DETAILS FOR PATIENTS

- Patient Support and Information Helpline: **0845 450 0375** (Monday to Friday from 10:00 to 16:00)
- Email support and information: **helpline@pituitary.org.uk**
- Endocrine Nurse Helpline (for medical information and support): **0845 450 0377** (Monday evenings from 18:00-21:00 and Thursday mornings from 9:00 to 13:00)

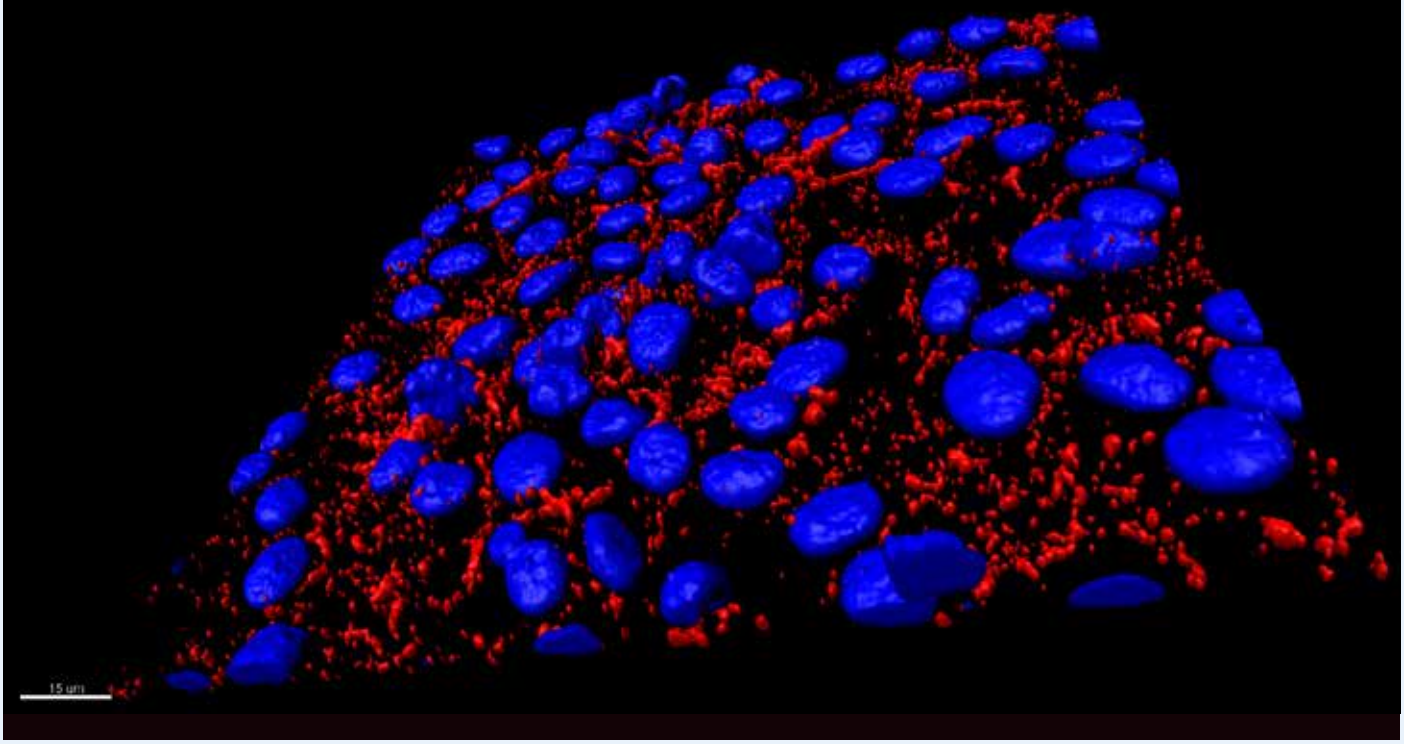
IMAGES IN ENDOCRINOLOGY

We hope you are inspired by this highlight from our journal Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM *ENDOCRINE-RELATED CANCER,* JUNE 2013

The image depicts thyrocytes cultivated on glass coverslips, immunostained for laminin (red) and nuclei (blue). Surface detail enhanced by confocal image analysis software.

Credit: **L Miranda-Alves, CY Palmero, CH Mendez, DP de Carvalho, T Coelho-Sampaio & LE Nasciutti,** Institute of Biomedical Sciences, Laboratory of Cellular and Molecular Endocrinology, Federal University of Rio de Janeiro, Brazil.



Enter our Cover Art Competition

for *Journal of Endocrinology, Journal of Molecular Endocrinology* and *Endocrine-Related Cancer.*

Visit **www.endocrinology.org/news** for more information.

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concentration
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Tostran® (testosterone) 2% Gel Prescribing Information Please refer to Summary of Product Characteristics (SPC) before prescribing. **Presentation** Tostran 2% Gel, contains testosterone, 20 mg/g. **Indications** Replacement therapy with testosterone for male hypogonadism when testosterone deficiency has been confirmed by clinical symptoms and laboratory analyses. **Posology** The starting dose is 3 g gel (60 mg testosterone) applied once daily at approximately the same time each morning to clean, dry, intact skin, alternately on the abdomen or to both inner thighs. Adjust dose according to clinical and laboratory responses. Do not exceed 4 g of gel (80 mg testosterone) daily. Apply after washing, bathing or showering. Do not apply to the genitals. Do not use in women, or children under the age of 18 years. **Contraindications** Known or suspected carcinoma of the breast or the prostate; hypersensitivity to any of the ingredients. **Special warnings and precautions for use** Tostran should not be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other aetiologies responsible for the symptoms have not been excluded. Not indicated for treatment of male sterility or sexual impotence. All patients must be pre-examined to exclude a risk of pre-existing prostatic cancer. Perform careful and regular monitoring of breast and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Oedema with/without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal or hepatic disease. Discontinue immediately if such complications occur. Use with caution in hypertension as testosterone may raise blood pressure. Use with caution in ischemic heart disease, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken with skeletal metastases due to risk of hypercalcaemia/hypercalcuria. Androgen treatment may result in improved insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety instructions. Health professionals/carers should use disposable gloves resistant to alcohols. **Interactions** When androgens are given simultaneously with anticoagulants, the anticoagulant effect can increase and patients require close monitoring of their INR. Concurrent administration with ACTH or corticosteroids may increase the likelihood of oedema and caution should be exercised. **Undesirable effects** Very common (≥1/10): application site reactions (including paresthesia, xerosis, pruritis, rash or erythema); common (≥1/100, <1/10): increased haemoglobin, haematocrit; increased male pattern hair distribution; hypertension; gynaecomastia; peripheral oedema; increased PSA. Certain excipients may cause irritation and dry skin. Consult SPC for other undesirable effects of testosterone. **Pack Size and Price** Packs containing one or three 60 g metered-dose canisters per pack. Price £26.67 per canister. **Legal Category** POM Further information is available from the **Marketing Authorisation Holder** ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, UK. **Marketing Authorisation Number** PL16508/0025 ©ProStrakan. ®Registered Trade Mark. Date of PI Preparation: March 2012.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard
Adverse events should also be reported to ProStrakan Limited on 01896 664000

References:
1. Dumas C. Poster presented at the 25th Scandinavian Meeting of Urology, Göteborg, June 2005 **2.** Tostran® Summary of Product Characteristics, March 2012 **3.** Testogel® Summary of Product Characteristics, November 2006 **4.** Testim® Summary of Product Characteristics, June 2011 **5.** MIMS February 2013.

M015/1194 Date of preparation February 2013

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